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The American Journal of CARDIOLOGY®

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Provocative Testing for Coronary Spasm

Comparison of Contrast and Radionuclide Angiography

Electrophysiologic Properties of Tocainide

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logical therapy for the vast
who need more or other



Logical therapy because essential hypertension is usually characterized by elevated peripheral resistance with normal cardiac output. ALDOMET lowers blood pressure apparently by lowering peripheral resistance—while cardiac output is usually maintained.

Appropriate for all degrees of hypertension when drug therapy is required

Highly effective in mild, moderate, or severe hypertension, ALDOMET (Methyldopa, MSD) is useful when there has been an inadequate response to initial thiazide therapy, or as initial therapy when thiazides are deemed inappropriate or contraindicated (for example, when hypersensitivity to sulfonamide-derived drugs exists).

Appropriate for many hypertensive patients requiring special consideration

- hypertensive patients with renal impairment—ALDOMET usually does not reduce glomerular filtration rate, renal blood flow, or filtration fraction. (Methyldopa is largely excreted by the kidney, and patients with impaired renal function may respond to smaller doses.)
- hypertensive children requiring drug therapy (See pediatric dosage recommendations in the addendum on the last page of this advertisement.)

P24, @113

Not contraindicated in the following coexisting conditions in which some other antihypertensives are contraindicated

- congestive heart failure (Edema may occur with ALDOMET. This is usually relieved by the use of a diuretic, but if edema progresses, methyldopa should be discontinued.)
- coronary artery disease (Aggravation of angina pectoris may occur with ALDOMET.)
- mitral valvular rheumatic heart disease
- bronchial asthma
- allergic rhinitis during the pollen season
- greater than first-degree heart block
- active peptic ulcer
- ulcerative colitis

majority of hypertensives
therapy than a thiazide...



Therapeutic limitations

ALDOMET is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previous methyldopa therapy has been associated with liver disorders.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, please see the brief summary of prescribing information.

TABLETS: 500 mg, 250 mg, and 125 mg

ALDOMET® (METHYLDOPA | MSD)

MSD
MERCK SHARP & DOHME

For a brief summary of prescribing information, please see following page.

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TABLETS: 500 mg, 250 mg, and 125 mg

ALDOMET®
(METHYLDOPA | MSD)

Logical therapy for the vast majority of hypertensives who need more or other therapy than a thiazide

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin-cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor.

Allergic: Drug-related fever, lupus-like syndrome, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 500.

For more detailed information, consult your MSD representative or see full prescribing information.

Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

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addendum

MSD MERCK SHARP & DOHME

DOSAGE INFORMATION ON ALDOMET® (Methyldopa | MSD)

Adults

initiating therapy

- 250 mg b.i.d. or t.i.d. the first 48 hours
- increase or decrease, preferably at intervals of not less than two days, until response is adequate
- start dosage increases in the evening to minimize sedation
- adjusting dosage may prevent morning hypotension without losing control of afternoon blood pressure
- when ALDOMET is added, the dosage of thiazides need not be changed
- when given with antihypertensives other than thiazides, the dose of these agents may have to be adjusted and the starting dosage of ALDOMET should be limited to 500 mg daily in divided doses

maintaining therapy

- usually 500 mg to 2.0 g daily in two to four doses
- maximum recommended daily dose is 3.0 g
- if effective control of blood pressure cannot be maintained on 2.0 g methyldopa daily and a thiazide is not already part of the regimen, a thiazide should be added
- occasional tolerance may occur, usually between the second and third month of therapy; adding a diuretic or increasing the dosage of ALDOMET frequently restores effective control
- patients with impaired renal function may respond to lower doses; syncope in older patients may be related to an increased sensitivity and advanced arteriosclerotic vascular disease and may be avoided by lower doses

Children

- initial dosage is based on 10 mg/kg of body weight daily in two to four doses
- increase or decrease daily dosage until adequate response is achieved
- maximum dosage is 65 mg/kg or 3.0 g daily, whichever is less

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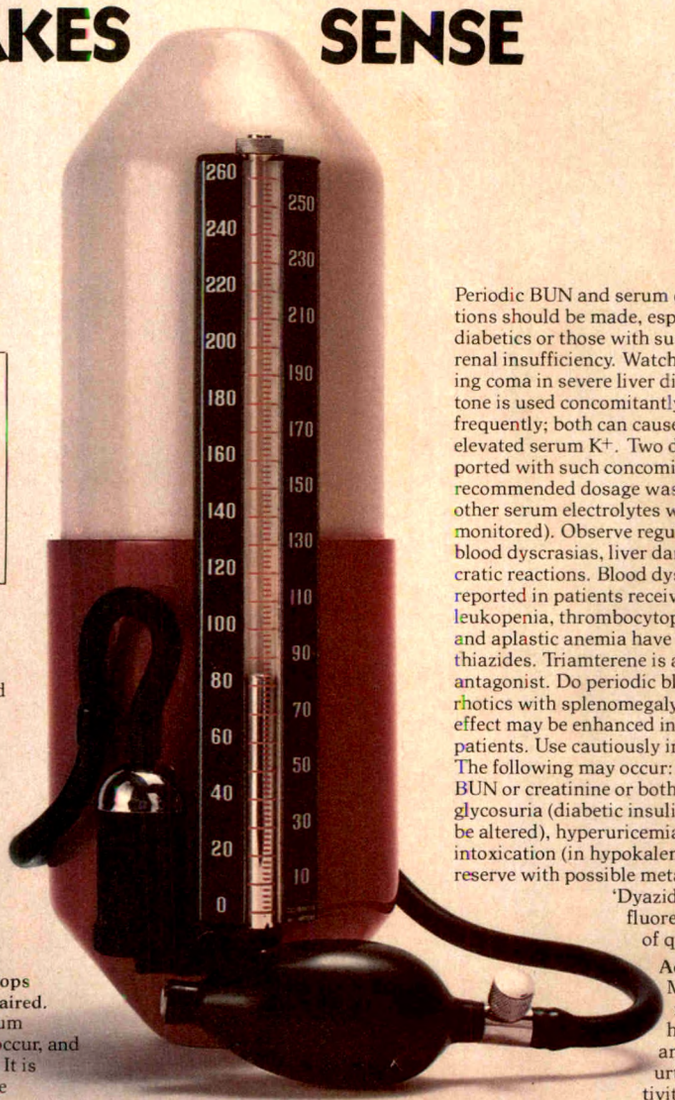
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* **Warning**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

* **Indications:** When the combination represents the dosage determined by titration: Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, the nephrotic syndrome. Corticosteroid and estrogen-induced edema, idiopathic edema; hypertension, when the potassium sparing action of triamterene is warranted. (See Box Warning.) Routine use of diuretics in healthy pregnant women is inappropriate; they are indicated in pregnancy only when edema is due to pathological causes.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

FOR LONG-TERM CONTROL OF HYPERTENSION.* SERUM K^+ AND BUN SHOULD BE CHECKED PERIODICALLY. (SEE WARNINGS SECTION.)

SK&F CO., Carolina, P.R. 00630

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- Well-tolerated, with few gastrointestinal disturbances to interfere with patient cooperation and compliance

Cooper Compliance Tip

Since most pharmacies have established patient drug profiles as a service to the community, you might advise your cardiac patients to use one pharmacy for all their prescription needs. This will help assure that the total therapeutic regimen is being carried out. Should any questions, untoward reactions or other problems develop, each person in the "physician-pharmacist-patient" alliance will be aware of it. Please forward your compliance tip to Cooper Laboratories, 300 Fairfield Road, Wayne, New Jersey 07470, Att: Mr. W.F. Cronin.

Patients with cardiac arrhythmias remember

Quinaglute® Dura-Tabs® (quinidine gluconate) 324 mg

Indications:
Premature atrial and ventricular contractions. Paroxysmal atrial tachycardia. Paroxysmal A-V junctional rhythm. Atrial flutter. Paroxysmal atrial fibrillation. Established atrial fibrillation when therapy is appropriate. Paroxysmal ventricular tachycardia when not associated with complete heart block. Maintenance therapy after electrical conversion of atrial fibrillation and/or flutter.
NOTE: Depending upon the response desired, the dosage may need to be varied and the blood level and/or electrocardiographic response closely monitored during initial treatment.

Contraindications: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.

Partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. Renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects; ventricular premature beats, ventricular tachycardia or flutter while on the drug. Marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis. Idiosyncrasy or hypersensitivity to quinidine.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate.

Precautions: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy.

Quinidine in large doses may reduce the contractile force of the heart; therefore, extreme caution should be exercised in using the drug in patients with severe heart disease, hypotension or digitalis intoxication.

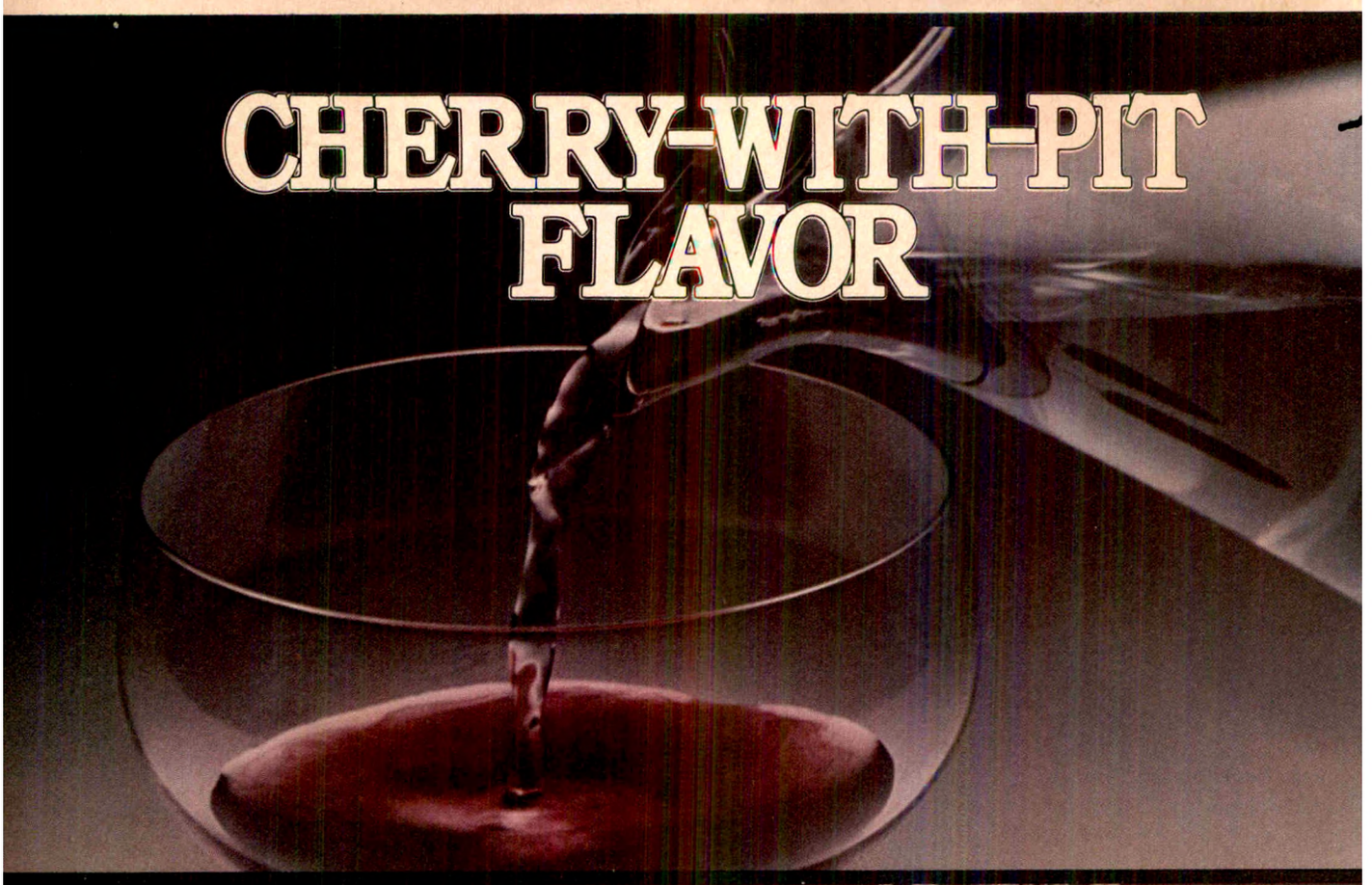
It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

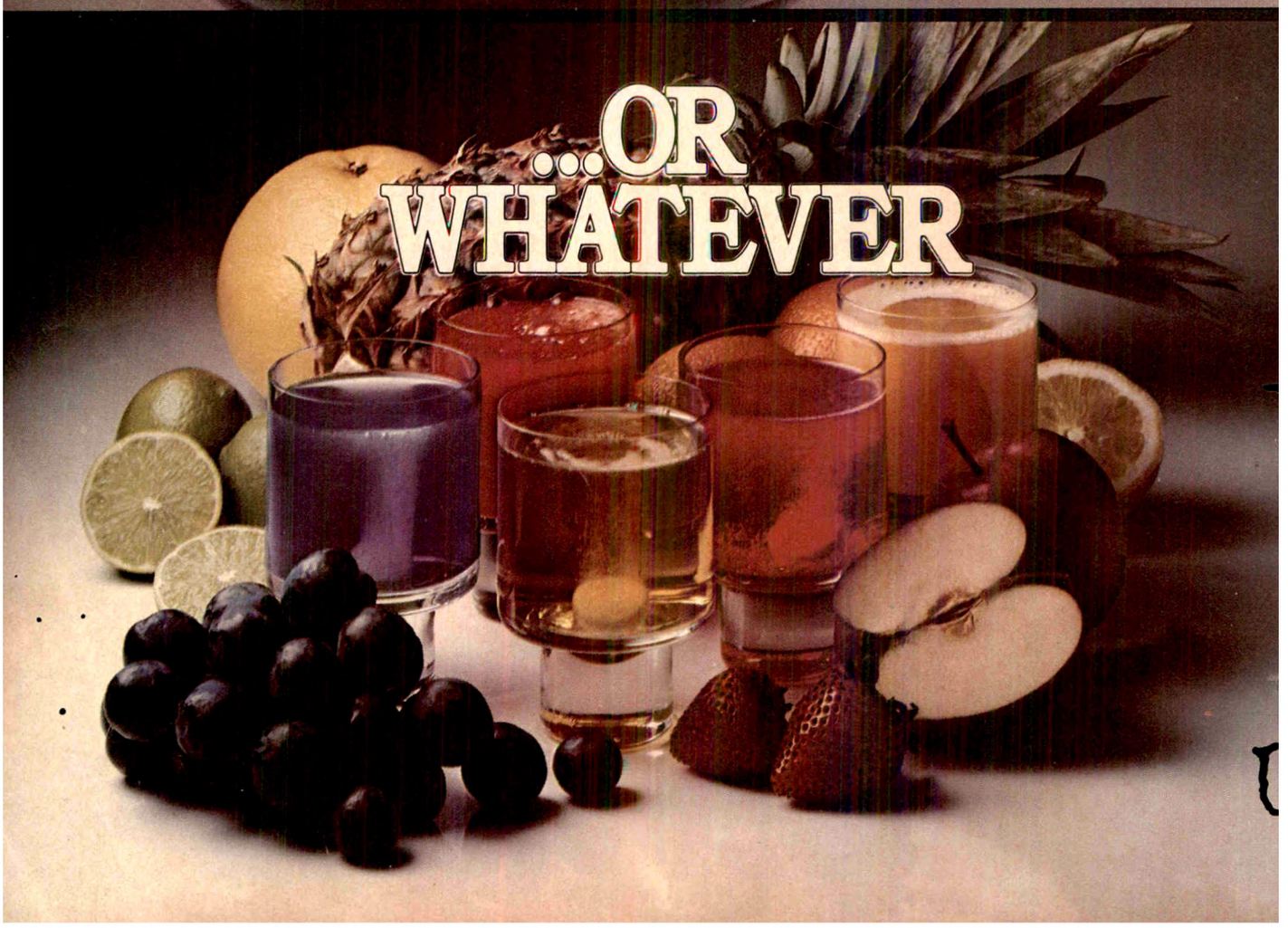
Adverse Reactions: Cinchonism, tinnitus, decreased auditory acuity, vertigo, headache, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis, hypotension, respiratory distress, and gastrointestinal disturbances.

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Convenience in therapeutic doses. Both forms of KLORVESS offer 20 mEq of potassium and chloride in each dose. There is no need to prescribe several slow-release tablets per dose or space dosage administration beyond the patient's normal routine. Prescribe KLORVESS Liquid or KLORVESS Effervescent Tablets . . . for potassium supplement therapy that offers good taste and convenience at therapeutic dosages.

Description: Klorvess Effervescent Tablets: Each dry, sodium- and sugar-free effervescent tablet contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g. Dissolution of the tablet in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

Indications: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

Contraindications: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements.

Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis.

High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest.

To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve each Klorvess Effervescent Tablet in 3 to 4 ounces of water or fruit juice, or dilute each tablespoonful of Klorvess (potassium chloride) 10% Liquid in 3 to 4 ounces of water. Both of these solutions should be ingested slowly with or immediately after meals.

Adverse Reactions: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts.

The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest.

The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

Dosage and Administration: Klorvess Effervescent Tablets: Adults—One Klorvess Effervescent Tablet (20 mEq each of potassium and chloride) completely dissolved in 3 to 4 ounces of cold water or fruit juice 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) of Klorvess Liquid (20 mEq of potassium chloride) completely diluted in 3 to 4 ounces of water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating. Deviations from these recommended dosages may be indicated in certain cases of hypokalemia based upon the patient's status. The average total daily dosage must be governed by the patient's response as determined by frequent evaluation of serum electrolytes, EKG and clinical status.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

Treatment of Hyperkalemia: 1. Dextrose solution, 10 or 25% containing 10 units of crystalline insulin per 20 g dextrose, given IV in a dose of 300 to 500 ml in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resins, orally and as retention enema. (Caution: Ammonium compounds should not be used in patients with hepatic cirrhosis.) 3. Hemodialysis and peritoneal dialysis. 4. The use of potassium-containing foods or medicaments must be eliminated. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

How Supplied: Klorvess Effervescent Tablets (white)—60 tablets (2 Rx units of 30 effervescent tablets each). Each tablet is individually foil wrapped. Klorvess (potassium chloride) 10% Liquid (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Tablets and Liquid are also available in institutional packaging as follows: Klorvess Tablets—30 and 1000 tablets; Klorvess Liquid—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

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APRIL 1978

The American Journal of CARDIOLOGY®

VOLUME 41

NUMBER 4

CONTENTS

CLINICAL STUDIES

631 **Ergonovine Maleate Provocative Test for Coronary Arterial Spasm**

FREDERICK A. HEUPLER, Jr., WILLIAM L. PROUDFIT, MEHDI RAZAVI, EARL K. SHIREY, RICHARD GREENSTREET and WILLIAM C. SHELDON

In this study group of 98 patients with either mild fixed obstructions of coronary luminal diameter (less than 50 percent) or normal coronary arteriograms, the ergonovine maleate provocative test proved a safe, sensitive and specific method for reproducing coronary spasm in patients with Prinzmetal's variant angina and no major coronary obstructions. Ten of the 11 patients with this syndrome had a positive test. Coronary spasm was not demonstrated in patients with normal coronary arteriograms and a history of myocardial infarction as an isolated clinical event or in the majority of patients with angina-like chest pain and no major coronary obstruction. When coronary spasm is suspected, coronary arteriography should be performed before the administration of nitroglycerin or atropine because premedication with vasodilators may mask spontaneous coronary spasm during angiography.

641 **Clinical Assessment of Serum Myosin Light-Chains in the Diagnosis of Acute Myocardial Infarction**

CHARLES A. TRAHERN, J. BREWSTER GERE, GARY H. KRAUTH and DARLENE A. BIGHAM

Human cardiac myosin light chains have been shown to be present in increased quantities in the serum of patients with myocardial infarction. This study quantitating serum myosin chain levels with radioimmunoassay in patients admitted to a coronary care unit found that this assay provides a biochemical marker of high sensitivity and specificity useful in the diagnosis of infarction. Values for human cardiac light chains in 84 patients without myocardial infarction were normal (less than 2 ng/ml) and in 29 patients with myocardial infarction were all elevated (average 10.9 ± 1.3 ng/ml; range 4 to 35 ng/ml). There were no false positive or false negative results. Additional studies to define the kinetics of the appearance and disappearance of the human cardiac myosin light chains from the serum in patients with myocardial infarction may lead to better means of quantitating infarct size.

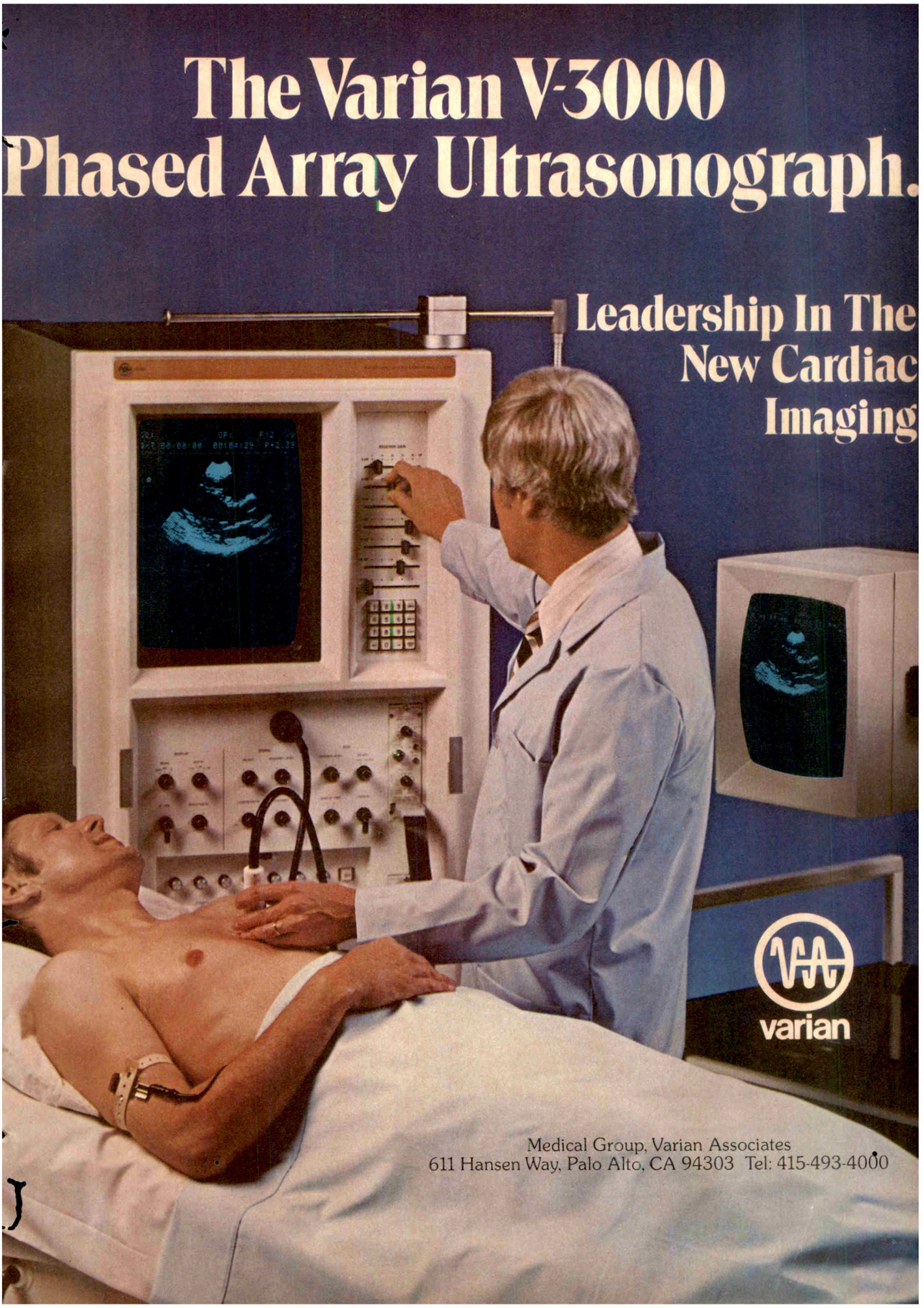
646 **Shape of the Human Cardiac Ventricles**

GROVER M. HUTCHINS, BERNADINE H. BULKLEY, G. WILLIAM MOORE, MARK A. PIASIO and FREDERICK T. LOHR

This topographic study of cardiac ventricles in 80 human hearts with and without ventricular dilatation or hypertrophy, or both, and normal coronary arteries and no myocardial lesions shows that ventricular configuration is a compromise between a spherical shape that needs the least energy for diastolic ventricular filling and a tubular shape that permits maximal conversion of systolic myocardial muscle cell tension into cavitary pressure increase. Ventricular topography probably develops as that geometry requiring the minimal energy expenditure in the overall economy of the circulation. The final shape of the human heart must further reflect an adaptation to the needs of both systole and diastole. Almost all forms of heart disease alter ventricular topography, and these changes in ventricular configuration may in themselves produce cardiac dysfunction. Hearts with predominant left hypertrophy have an increase in the average curvature-thickness index of all three segments of the wall. The major factor leading to the greater indexes is increased wall thickness, which is accompanied by an overall average doubling of weight and increase in ventricular length and diameter but no change in ventricular volume. The heart with chronic dilatation shows a decreased index and, compared with the normal heart and the heart with left ventricular hypertrophy, has a wall too thin for the ventricular size.

Continued on page A14

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1 In the hypertensive patient, 1.06 grams of retained sodium* can cause a 300 ml. expansion of fluid volume, which can increase blood volume by 100 ml., or 2%.

2 A chronic 2% increase in blood volume can lead to as much as a 24 to 46 mm. Hg increase in diastolic blood pressure.†

3 Diuretics reduce blood pressure by blocking the renal retention of sodium and water. To assure continuous control of hypertension, many leading medical authorities have concluded that this action should be sustained around the clock.[2-5]

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*All values given in this example are approximations based on standard physiologic data and solute-volume relationships.

†From a baseline of 80 mm. Hg diastolic.

BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema.

Contraindications: Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.

Warnings: Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.

Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

Adverse Reactions: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

Usual Dose: One tablet daily.

How Supplied: Tablets—100 mg. (white, scored) and 50 mg. (aqua) in bottles of 100 and 1000; PAKs of 28 tablets, boxes of 6, unit-dose blister packs, boxes of 100 (10 x 10 strips).

References:

1. Guyton, A.C.: Regulation of arterial pressure: II. The renal-body fluid system for long-term pressure control. Mechanisms of hypertension, in Textbook of Medical Physiology, Philadelphia, Saunders, 1976, p. 281. **2.** Kaplan, N.: Treating hypertension: The results are in, in Mandates Hypertension (Kaplan, N.M., ed.), New York, Medcom, 1976, p. 6. **3.** Finnerty, F.A., Jr.: Hypertension: The Continuing Challenge, Scientific Exhibit, Meeting of AAFP, Boston, Mass., Sept. 20-23, 1976. **4.** Fries, E.D.: The treatment of hypertension: Why, when and how, in Hypertension Manual (Laragh, J.H., ed.), New York, Dun-Donnelley, 1974, p. 751. **5.** Tarazi, R.C.: Modern concepts in diuretic therapy, Postgrad. Med. 56:37, 1974.

CONTENTS

55 **Continuous Ventricular Dimensions in Man During Supine Exercise and Recovery. An Echocardiographic Study**

RICHARD A. STEIN, DONALD MICHIELLI, EDWARD L. FOX and NORMAN KRASNOW

Using continuous echocardiographic recording to define the left septal and left ventricular posterior endocardial walls, these investigators studied the left ventricular internal dimensions of 10 healthy men aged 18 to 23 years during supine bicycle ergometer exercise. The subjects were not conditioned to exercise by regular athletic programs. During constant mild work load exercise of about 35 percent of the predicted maximum, end-diastolic dimension did not change, end-systolic dimension decreased insignificantly by 4 percent and stroke dimension and fractional shortening of the ventricular dimension rose 7 and 5 percent, respectively. During the recovery phase of supine exercise there was a significant increase in end-diastolic and stroke dimensions and a parallel rise in the percent shortening of the ventricular dimensions. During exercise a clear Frank-Starling effect is masked; during recovery there is a transient increase in end-diastolic volume and a measurable Frank-Starling effect.

61 **Myocardial Structure and Function in Patients With Aortic Valve Disease and Their Relation to Postoperative Results**

FRANZ SCHWARZ, WILLEM FLAMENG, JUTTA SCHAPER, FRIEDERIKE LANGEBARTELS, JOCHEN THORMANN, FRITZ HEHRLEIN and MARTIN SCHLEPPER

Designed to determine the significance of interstitial myocardial fibrosis and degenerative cell changes in patients with aortic valve disease after aortic valve replacement, this study of 21 patients suggests that depressed left ventricular function in aortic valve disease is associated with ultrastructural degenerative cell changes, but complete recovery of cardiac function after operation is not prevented by these changes. Furthermore, interstitial myocardial fibrosis is not a primary determinant of depressed cardiac function in such disease. Before operation, patients with aortic valve disease had a significantly higher left ventricular mass than control subjects and a lower ejection fraction and mean normalized systolic ejection rate; after operation, left ventricular mass decreased considerably and ejection fraction and mean normalized systolic ejection rate became normal. Such restoration of depressed myocardial function after aortic valve replacement strongly suggests that these ultrastructural myocardial changes are fully reversible and that the generally accepted term "degenerative" is probably not adequate.

70 **Diagnostic Value of Exercise-Induced S-T Segment Depression in Patients With Right Bundle Branch Block**

TOSHIHIDE TANAKA, MARK J. FRIEDMAN, ROBERT D. OKADA, LARRY J. BUCKELS and FRANK I. MARCUS

Twelve lead submaximal treadmill exercise testing in 30 patients with right bundle branch block, mainly men with symptoms of ischemic heart disease, showed a sensitivity rate of 69 percent and a specificity rate of 45 percent in detecting coronary artery disease in the presence of right bundle branch block. The specificity was greater if S-T depression was recorded in leads V_4 to V_6, whereas S-T segment depression limited to leads V_1 to V_3 often represented a false positive exercise test.

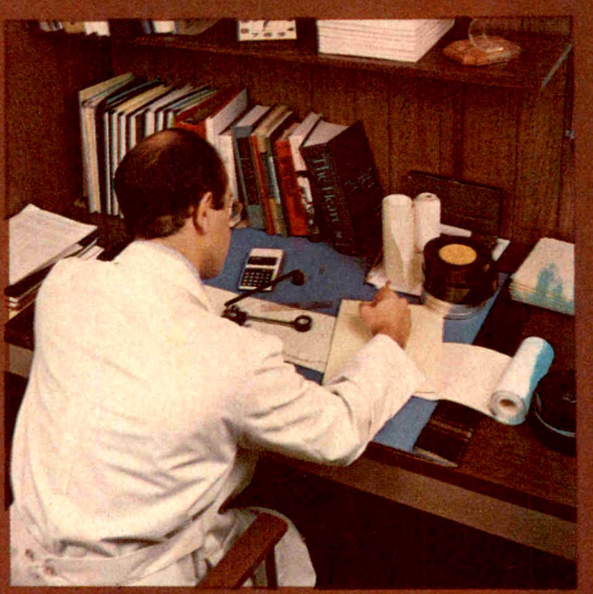
74 **Early Identification of Patients Developing Late In-Hospital Ventricular Fibrillation After Discharge From the Coronary Care Unit. A 5 1/2 Year Retrospective and Prospective Study of 1,897 Patients**

K. I. LIE, KOEN L. LIEM, REINIER M. SCHUILENBERG, GEORGE K. DAVID and DIRK DURRER

This 5 1/2 year retrospective and prospective study of 1,897 patients with acute myocardial infarction demonstrated that coronary care unit survivors with anteroseptal infarction complicated by right or left bundle branch block had a significant incidence of late in-hospital ventricular fibrillation and should be kept in the monitoring area for 6 weeks. The total incidence of late ventricular fibrillation was 35 percent in the retrospective study and 36 percent in the prospective study. Additional significant factors related to the development of late in-hospital ventricular fibrillation included peak SGOT level, heart failure during the coronary care unit stay, persistent sinus tachycardia, supraventricular tachycardia and pericarditis. A ventricular aneurysm was found at autopsy in 18 patients who died with recurrent attacks of ventricular fibrillation in the retrospective study. Long-term monitoring with earlier initiation of cardiopulmonary resuscitation and prophylactic antiarrhythmic therapy in this high risk group of patients with acute anteroseptal wall myocardial infarction and left or right bundle branch block merits further investigation.

Continued on page A17

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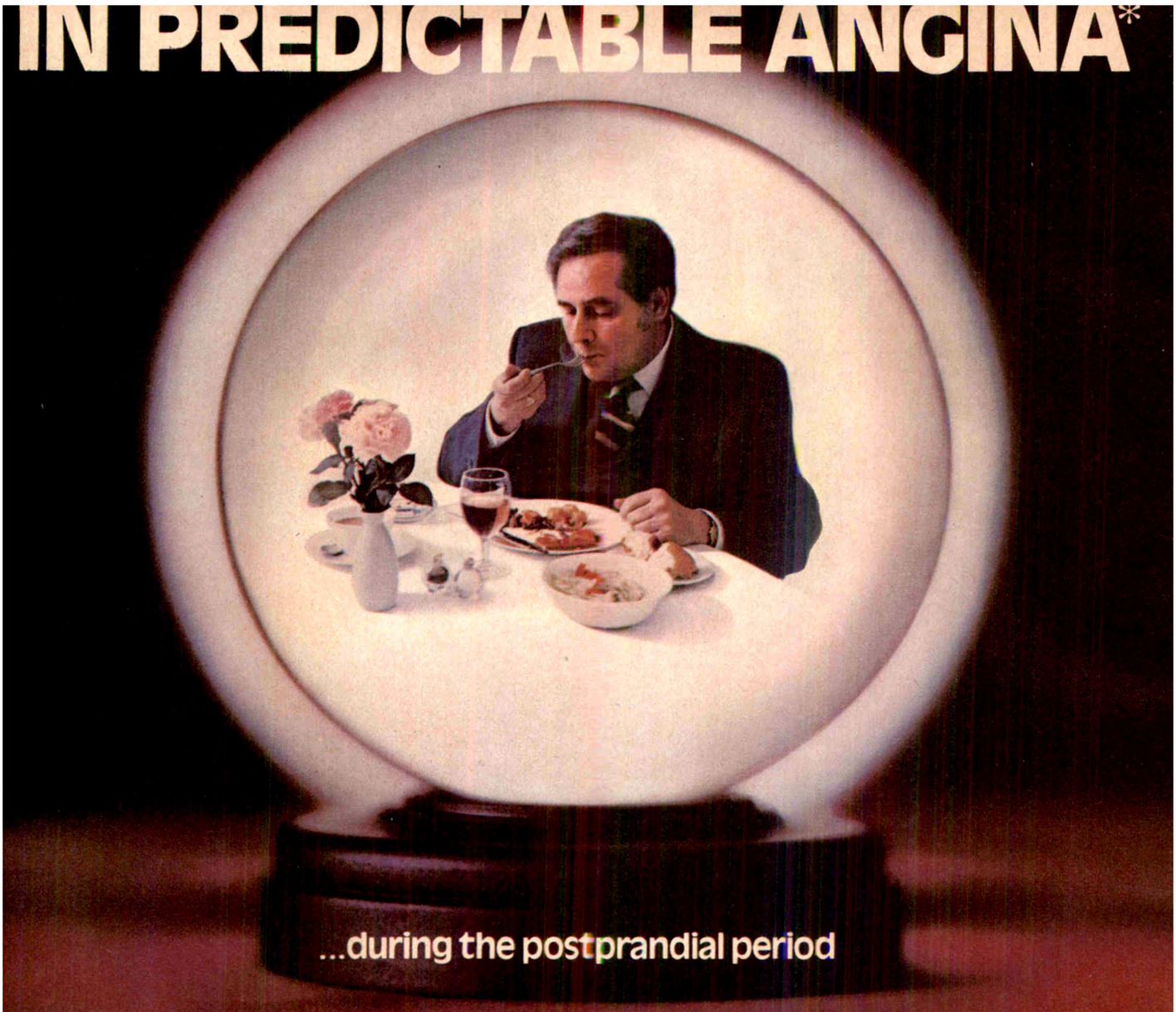
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"Probably" effective: The chewable dosage form of SORBITRATE is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classifications of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.

Precautions: Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing, transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: *Individual Dose:* To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg.

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CONTENTS

678 **Initiation of Repetitive Ventricular Depolarizations by Relatively Late Premature Complexes in Patients With Acute Myocardial Infarction**

ROBERT ROBERTS, H. DIETER AMBOS, CHRISTOPHER W. LOH and BURTON E. SOBEL

Early premature ventricular complexes accounted for only 38 percent of the total premature ventricular complexes recorded by continuous electrocardiographic monitoring during the first 10 hours in 38 patients with acute myocardial infarction and no shock. The more prevalent late premature ventricular contractions were found to initiate 78 percent of 337 episodes of repetitive ventricular depolarizations in 29 patients and all episodes in 22 patients, attesting to their potential importance as warning arrhythmias and precipitants of malignant arrhythmias that may require pharmacologic suppression. It is possible that the treatment with lidocaine initiated these repetitive ventricular depolarizations or that early or late premature ventricular contractions, or both, may be manifestations of an underlying electrophysiologic instability of the heart that gives rise to repetitive ventricular depolarizations independently. The ventricular arrhythmias in these patients are ascribed to automaticity rather than reentry.

684 **Time-Related Changes in the Q-T Interval in Acute Myocardial Infarction: Possible Relation to Local Hypocalcemia**

ROBERT M. DOROGHAZI and RORY CHILDERS

These results outline a "natural history" for the Q-T interval after acute myocardial infarction. In 63 patients with either acute transmural or nontransmural myocardial infarction, the Q-T interval was prolonged beyond normal limits on at least 1 of the 5 days after infarction in 27 patients (8 with transmural and 19 with nontransmural infarction). The Q-T duration returned to normal by the sixth day after infarction in all patients whose Q-T interval lengthened beyond normal limits, regardless of the magnitude of prolongation. In patients with nontransmural infarction Q-T prolongation may possibly prove useful in the diagnostic separation of ischemia from actual necrosis, when the electrocardiogram shows only T wave inversion. Possible causes of such Q-T prolongation are local hypothermia, local conduction delay, neurogenic effect and local hypocalcemia, the latter being most significant.

EXPERIMENTAL STUDIES

689 **Improvement by Propranolol of Regional Myocardial Dysfunction and Abnormal Coronary Flow Pattern in Conscious Dogs With Coronary Narrowing**

HITONOBU TOMOIKE, JOHN ROSS, Jr., DEAN FRANKLIN, BERTRAND CROZATIER, DANIEL McKOWN and W. SCOTT KEMPER

After the administration of propranolol during partial coronary arterial constriction in conscious resting dogs, heart rate decreased to 72 ± 4 from 95 ± 4 beats/min, contraction in the ischemic segment and left ventricular wall thickening increased markedly and coronary flow returned to a normal velocity pattern. These favorable effects were only partially diminished by cardiac pacing to increase the heart rate to that before treatment with propranolol. After release of the stenosis reactive hyperemia occurred, and by 10 minutes the flow pattern was normal with mild residual depression of ischemic segment shortening. It seems likely that the dominant effect produced by propranolol was a reduction in myocardial oxygen requirements effected by slowing, to a rate below control level, the moderate tachycardia that accompanies coronary constriction and may be reflex in origin. Other factors such as redistribution of coronary blood flow are also operative.

697 **Recording From the Body Surface of Arrhythmogenic Ventricular Activity During the S-T Segment**

EDWARD J. BERBARI, BENJAMIN J. SCHERLAG, RONALD R. HOPE and RALPH LAZZARA

This preliminary study shows that the S-T segment of the precordial electrocardiogram contains more information than previously suspected. It reports the results of a method using high amplification, band pass filtering and signal averaging to record from the body surfaces of dogs the delayed epicardial potentials that are the result of ischemia and are associated with the onset of ventricular arrhythmias. This study demonstrates how signal averaging can detect such reentrant activity from the body surface. These potentials are in the microvolt range and are not recorded in the standard electrocardiogram. The extension of similar signal averaging techniques to man may become a noninvasive diagnostic method of measuring the prodrome of ventricular arrhythmias.

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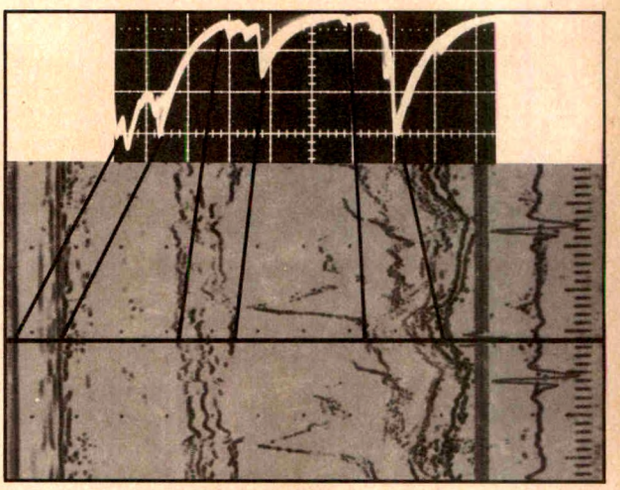
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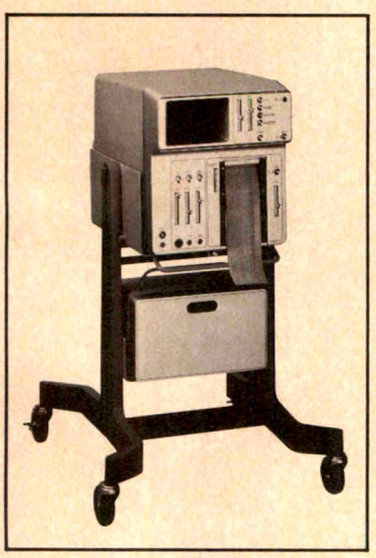


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703 **Electrophysiologic Properties of a New Antiarrhythmic Drug—Tocainide**

E. NEIL MOORE, JOSEPH F. SPEAR, LEONARD N. HOROWITZ, HAL S. FELDMAN and ROBERT A. MOLLER

Tocainide, an orally active antiarrhythmic drug structurally related to lidocaine, abolished ventricular ectopic activity induced by ouabain in isolated canine Purkinje fibers and in intact dogs and by coronary arterial ligation in the latter. It also increased the ventricular fibrillation threshold during normal supraventricular rhythm and after premature ventricular beats and depressed atrioventricular nodal conduction. Tocainide slows conduction of premature beats by its effect on the membrane responsiveness curve. The toxic effects of up to twice the therapeutic concentrations effective in suppressing arrhythmias caused by digitalis toxicity and myocardial infarction were minimal. These and other results showing that tocainide has definite antiarrhythmic activity, minimal side effects and a long therapeutic half-life indicate that it is a promising antiarrhythmic agent and deserves further study in patients.

METHODS

710 **"Ventricular Function Curve" From a Single Diagnostic Left Ventriculogram: Technique, Results and Value**

MARK J. MORTON, JOHN H. McANULTY and SHAHBUDIN H. RAHIMTOOLA

This paper describes a method that allows one to obtain several different end-diastolic volumes and stroke volumes from a single diagnostic ventriculogram using a programmable atrial pacemaker to vary sequential left ventricular end-diastolic volumes. Left ventricular stroke volume and end-diastolic volume were used to construct a left ventricular "function curve." This study demonstrated that the ejection fraction depends on end-diastolic volume with rapid changes of R-R interval. Both ejection fraction and end-diastolic volume should be measured when the ejection fraction is used as an index of left ventricular performance, particularly if ejection fractions obtained from different angiograms are being compared.

718 **Quantitative Radionuclide Angiography in the Right Anterior Oblique View: Comparison With Contrast Ventriculography**

MONTY M. BODENHEIMER, VIDYA S. BANKA, COLLEEN M. FOOSHEE, GEORGE A. HERMANN and RICHARD H. HELFANT

Comparison of first pass radionuclide angiography in the right anterior oblique view with contrast ventriculography in 44 patients undergoing evaluation for coronary disease shows that this technique, despite limitations because of current technology, is a sensitive noninvasive means of assessing the location and severity of asynergy and global ventricular performance in these patients. First pass radionuclide angiography performed in the right anterior oblique view permits accurate assessment of the wall motion of areas of the left ventricle suboptimally seen in other views and permits determination of the left ventricular ejection fraction. This technique permits temporal separation of the right and left ventricles and obviates the problem of anatomic overlap of the right and left ventricles in the right anterior, apical and inferior segments along the long axis of the left ventricle.

726 **Estimation of Left Ventricular Volumes in Man From Biplane Cineangiograms Filmed in Oblique Projections**

JOSHUA WYNNE, LAURENCE H. GREEN, TIFT MANN, DAVID LEVIN and WILLIAM GROSSMAN

Biplane right and left anterior oblique cineventriculograms of left ventricular casts from 11 specimens of postmortem hearts of patients without heart disease and of 17 hearts in normal living subjects are used to validate the use of biplane oblique left ventriculography as a method of assessing true left ventricular volume. If the particular regression equation developed in this study is to be utilized, strict standardization of the degree of obliquity (30° right and 60° left anterior oblique) is required to offset variation in the long axis in the left anterior oblique projection caused by foreshortening.

Continued on page A22

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733 **Modification of Intraaortic Balloon Catheter to Permit Introduction by Cardiac Catheterization Techniques**

STEVEN WOLFSON, DENNIS L. KARSH, RENE A. LANGOU, ALEXANDER S. GEHA, GRAEME L. HAMMOND and LAWRENCE S. COHEN

An intraaortic balloon, modified by adding a central lumen to permit pressure monitoring, injection of contrast medium and passage of a guide wire, was successfully used in 15 of 16 patients, including 4 of 5 in whom attempts to place a standard balloon catheter had failed. This modified catheter increases the efficacy and safety of insertions and allows immediate and continuous monitoring of arterial pressure. Only transient signs of limb ischemia or arterial occlusion were noted, and they probably were due to spasm of the artery or obstruction of blood flow by the catheter itself. No permanent complications occurred and no embolic phenomena were detected.

PEDIATRIC CARDIOLOGY

739 **Ebstein's Anomaly of the Heart Revisited**

KENNETH R. ANDERSON and J. T. LIE

Based on the study of 15 well preserved autopsy specimens, this reappraisal of Ebstein's anomaly suggests that abnormal embryonic development of the right atrioventricular (A-V) junction may be the primary event leading to malformation of the tricuspid valve apparatus. Enlargement of the right A-V junction was consistently found in all specimens. However, the reason for such enlargement remains elusive. Some dilatation of the right ventricle is also an integral part of Ebstein's anomaly associated with and possibly due to deficiency of the myocardium of the right ventricle. These and other integral components of the congenital malformation complex of Ebstein's anomaly should be considered in designing or carrying out the surgical correction of this congenital heart condition. Massive dilatation of the right ventricle, when present, may be a limiting factor in achieving good results with such surgical repair.

746 **Discrete Subaortic Stenosis in Newfoundland Dogs: Association of Infective Endocarditis**

WALINJOM F. T. MUNA, VICTOR J. FERRANS, JOSEPH E. PIERCE and WILLIAM C. ROBERTS

Fatal infective endocarditis involving the aortic valve occurred in four of eight Newfoundland dogs from the same colony with discrete subaortic stenosis. Damage to the aortic valve cusps by the jet of blood ejected through the discretely narrowed left ventricular outflow tract predisposes to the development of infective endocarditis in dogs and human beings with discrete subaortic stenosis. Luminal narrowing, intimal fibrous proliferation, medial hypertrophy and medial smooth muscle disorganization were noted in many intramural coronary arteries in the ventricular septum of all eight dogs. Although these alterations suggest a similarity between discrete subaortic stenosis and hypertrophic cardiomyopathy, other differences described in this study indicate that each is a distinctly separate entity.

755 **Pathogenesis of Persistent Truncus Arteriosus in Light of Observations Made in a Dog Embryo With the Anomaly**

LODEWYK H. S. VAN MIEROP, DONALD F. PATTERSON and WILLIAM R. SCHNARR

These detailed observations on an embryo with persistent truncus arteriosus, type I and a crown-rump length of 20 mm obtained from a strain of Keeshond dogs known for spontaneously occurring conotruncal anomalies support the view that in persistent truncus arteriosus there is failure of septation of the truncus arteriosus. This specimen had a dysplastic, quadricuspid truncal valve; the truncus cushions were hypoplastic and had failed to fuse, and each had simply produced an arterial cusp. Other associated anomalies included a right subclavian artery arising anomalously from the descending aorta, a single coronary artery, an absent ductus arteriosus and a small persistent left cranial (superior) vena cava.

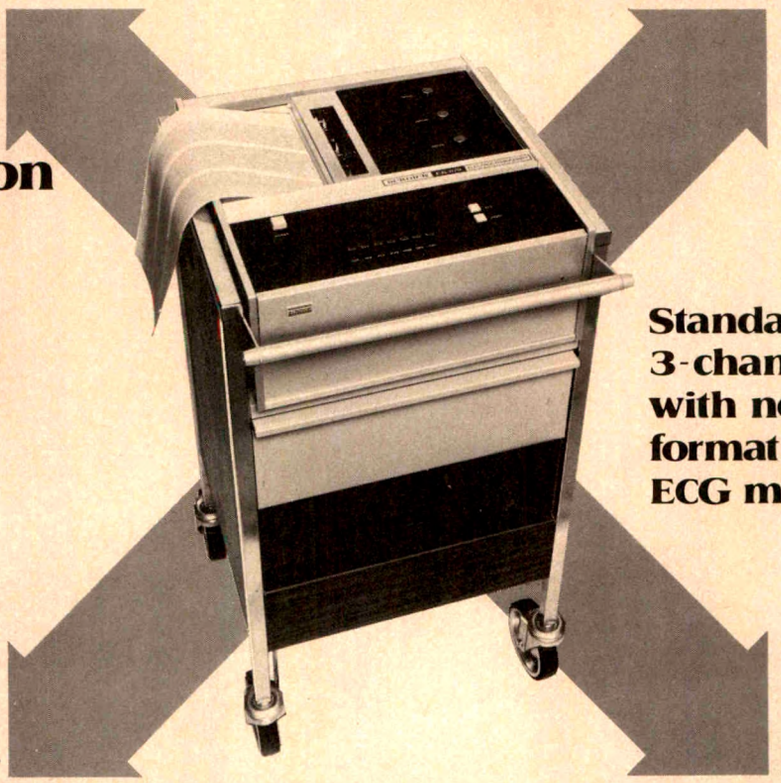
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REPORTS ON THERAPY

763 Electrophysiologic Effects of Hydralazine on Sinoatrial Function in Patients With Sick Sinus Node Syndrome

TOBY R. ENGEL, CHERYL LEDDY, ANA DEL GONZALEZ, STEVEN G. MEISTER and WILLIAM S. FRANKL

These data suggest that hydralazine is useful in the treatment of hypertension in the patient with sick sinus node syndrome and may possibly be efficacious in patients with this syndrome and normal blood pressure. In this study of the electrophysiologic effects of hydralazine in nine hypertensive patients with sinoatrial dysfunction, intravenous hydralazine (0.15 mg/kg) caused no significant reduction in arterial blood pressure, increased heart rate and shortened sinus nodal recovery time and second escape cycles. A minimal blood pressure response to hydralazine was associated with enhanced automaticity. These effects of hydralazine on automaticity could not be explained by a reflex response to decreased blood pressure and are attributed to its central or direct cardioaccelerator effects.

770 Single and Multiple Dose Pharmacokinetics of Oral Quinidine Sulfate and Gluconate

HERMANN R. OCHS, DAVID J. GREENBLATT, ELAINE WOO, KATE FRANKE, HENRY J. PFEIFER and THOMAS W. SMITH

This study in healthy volunteers provides a framework for understanding the pharmacokinetic differences between oral quinidine sulfate and gluconate and their implications for antiarrhythmic therapy. The apparent systemic availability of quinidine sulfate averaged 85 percent, and that of quinidine gluconate 75 percent, apparently reflecting less complete gastrointestinal absorption of the gluconate salt. Peak serum quinidine levels after single oral doses of quinidine gluconate averaged 60 percent less and were reached 2 hours later than with quinidine sulfate. The results of the multiple dose trial generally were consistent with the single dose findings. Administration of quinidine sulfate every 6 hours yielded maximal serum concentrations averaging 67 percent higher than the minimal concentration. For quinidine gluconate given every 12 hours, the maximal concentration averaged 70 percent higher than the minimal concentration. The slow absorption of quinidine from the gluconate preparations allows maintenance therapy on a 12 hourly dosage schedule with acceptable interdose fluctuation in serum levels.

778 Propranolol Rebound—A Retrospective Study

ROBERT A. SHIROFF, JAMES MATHIS, ROBERT ZELIS, DENNIS W. SCHNECK, JOSEPH D. BABB, DAVID M. LEAMAN and ARTHUR H. HAYES, Jr.

This study concludes there is little risk (2 to 3 percent) of propranolol rebound syndrome (an increase in the number or severity of anginal attacks, appearance of unstable or crescendo angina, myocardial infarction or death after abrupt cessation of propranolol) in patients with symptomatic coronary artery disease if clinical circumstances require abrupt stopping of propranolol therapy, provided physical activity is significantly curtailed. In 55 patients who discontinued propranolol therapy abruptly before cardiac catheterization there were no deaths, one myocardial infarction attributed to catheterization and one instance of change in pain pattern. Nevertheless, it seems prudent to gradually reduce the drug dosage of propranolol for several days before withdrawing the drug in patients with psychologic stress preparing to undergo open heart surgery. The mechanism of propranolol rebound remains unknown.

CASE REPORTS

781 Effusive-Constrictive Hemodynamic Pattern Due to Neoplastic Involvement of the Pericardium

TIFT MANN, BRUCE R. BRODIE, WILLIAM GROSSMAN and LAMBERT McLAURIN

- This study demonstrates that direct myocardial or visceral pericardial invasion by tumor is not uncommon and can be hemodynamically demonstrated by right heart catheterization performed in association with pericardiocentesis in patients with suspected malignant cardiac tamponade. Six of eight patients demonstrated the hemodynamic features of subacute effusive-constrictive pericarditis manifested by a persistently elevated right atrial pressure after pericardiocentesis when intrapericardiac pressure had returned to normal. Cardiac compression

Continued on page A26

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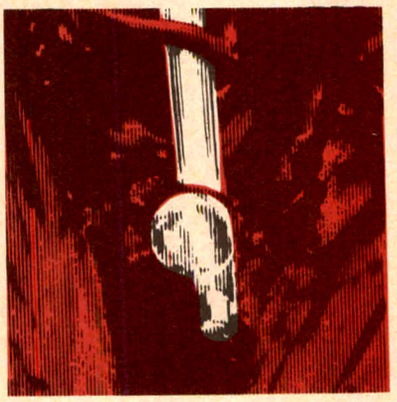
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in these patients results from both a large pericardial effusion and visceral pericardial constriction or myocardial restriction. Two of the eight patients with evidence of pericardial effusion on echocardiography but little or no fluid at pericardiocentesis apparently represent one end of a spectrum of effusive-constrictive involvement with constriction due to tumor as the predominant cause of cardiac dysfunction.

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787 Coronary Arterial Spasm and Provocative Testing in Ischemic Heart Disease
RICHARD H. HELFANT

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790 Letters to the Editor

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Cardiac Output and Pulmonary Vascular Resistance in Hypertension—K. R. T. Tyson and J. M. Atkins

Quinidine Dementia—G. J. Gilbert

Propranolol, P_{50} and Oxygen Delivery—S. H. Humphrey, B. R. Alter and S. Wolfson, et al.

Wrapping of Aortic Aneurysm—F. Robicsek and C. E. Anagnostopoulos

Heart Rate After Atropine—A. J. Swaminathan and W. F. C. Duvernoy

Reduction of Sudden Death by Aortocoronary Bypass Surgery—I and II—T. A. Preston, D. A. Spodick and H. N. Hultgren, et al.

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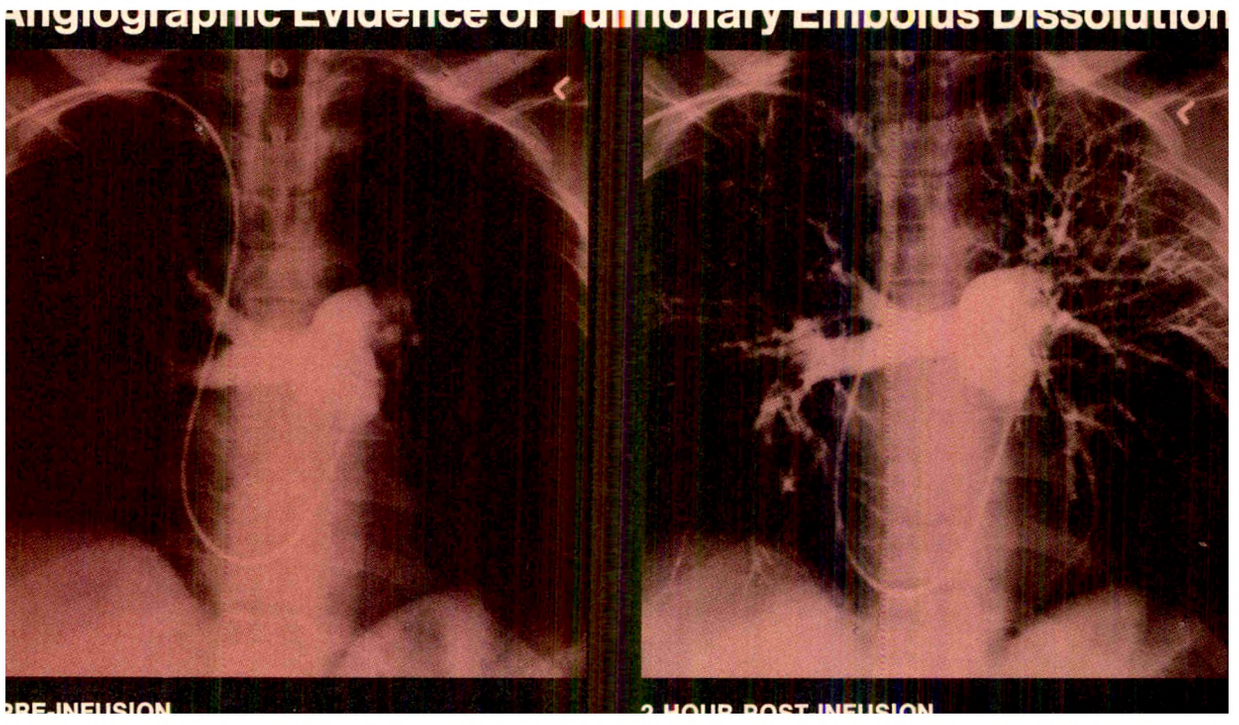
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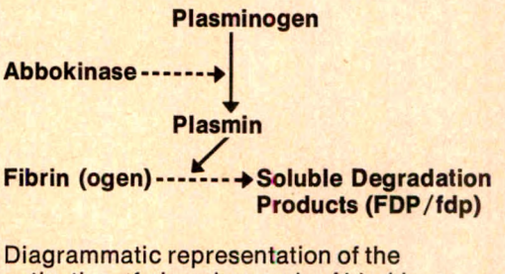
A unique thrombolytic agent for the management of acute massive pulmonary embolism

Acute massive pulmonary embolism is a catastrophic phenomenon. It is estimated that between 140,000 and 200,000 persons die each year as a result of pulmonary embolism. Previously, anticoagulants or surgery have been the only measures available to the physician to combat this condition.

The introduction of Abbokinase represents a significant addition to the limited therapeutic armamentarium available for the management of acute massive pulmonary embolism. While not without risks, thrombolytic therapy has proven capable of producing rapid dissolution of pulmonary emboli with prompt improvement of hemodynamic parameters.

A new generation of thrombolytic agents

Abbokinase acts on the endogenous fibrinolytic system by converting plasminogen to the proteolytic enzyme, plasmin. Plasmin, in turn, degrades fibrin clots as well as fibrinogen and other plasma proteins.[1] The plasmin is rapidly inactivated by a variety of naturally occurring plasma inhibitors.[2] Since plasminogen is present in the thrombus/embolus, activation by Abbokinase occurs within the thrombus/embolus as well as on its surface.[3]

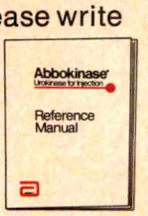


Diagrammatic representation of the activation of plasminogen by Abbokinase, and the degradation of fibrin (ogen) by plasmin.

Abbokinase is not a foreign protein. Originally derived from human urine, it is now obtainable from human kidney cells by tissue culture techniques developed by Abbott Laboratories.

Unlike streptokinase, Abbokinase has been associated with few allergic responses. Induced antibody formation is not seen in intradermal tests.

To make Abbokinase readily available throughout the U.S., it initially will be distributed from North Chicago, Illinois and 45 strategically located hospitals. For a copy of the ABBOKINASE REFERENCE MANUAL, please write Medical Services Department, Abbott Laboratories, Pharmaceutical Products Division, North Chicago, Ill. 60064.



8013241

References

1. McNicol, G. P., The Fibrinolytic Enzyme System, *Postgraduate Medicine*, August, 1973 (supplement). **2.** Aoki, N., et al, The Behavior of a 2-Plasmin Inhibitor in Fibrinolytic States, *Journal of Clinical Investigation*, 60:361-369, 1977. **3.** Chesterman, C. N., et al, Relationship of Plasminogen Activator to Fibrin, *Nature* (New Biol.), 238:15-17, 1972.

Please see following page for Brief Summary

ABBOTT

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Brief Summary

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ABBOKINASE (urokinase for injection) should only be used by physicians with wide experience in the management of thrombotic disease in hospitals where the recommended clinical and laboratory monitoring (see WARNINGS, PRECAUTIONS and DOSAGE AND ADMINISTRATION) can be performed.

When considering treatment with urokinase, the physician should carefully assess the overall clinical status and history of the patient. The hemostatic capability of the patient is more profoundly altered and bleeding more frequent with urokinase therapy than with heparin or oral coumarin anticoagulant therapy. When bleeding occurs it is also more severe and more difficult to manage. The potential risk of serious hemorrhage relative to such factors as age, physical condition, and underlying bleeding tendency of the patient (as described under WARNINGS and PRECAUTIONS) should be weighed against the potential benefits of treating the patient with urokinase.

INDICATIONS

Pulmonary Embolism

ABBOKINASE (urokinase for injection) is indicated in adults:

- for the lysis of acute massive pulmonary emboli, defined as obstruction or significant filling defects involving two or more lobar pulmonary arteries or an equivalent amount of emboli in other vessels.[8]
- for the lysis of pulmonary emboli accompanied by unstable hemodynamics, i.e., failure to maintain blood pressure without supportive measures.

The diagnosis should be confirmed by objective means, preferably pulmonary arteriography.

Urokinase treatment should be instituted as soon as possible after onset of pulmonary embolism, and no later than five days after onset. Under these circumstances, angiographic and hemodynamic measurements demonstrate a more rapid improvement during the first 24 hours of therapy than with heparin therapy (Table I).[7-9] However, it has not been established that treatment with urokinase decreases morbidity or mortality, when compared to heparin therapy alone.

TABLE I †

	UPET*		USPET**	
	Heparin	12-Hour Urokinase	12-Hour Urokinase	24-Hour Urokinase
Change in angiographic severity score based on 4-point system	0.54	1.78	1.66	1.76
Decrease in relative percentage perfusion defect on lung scans	8.3	24.1	20	29.2
Change in pulmonary artery pressure (mm Hg)	—1.1	—6.2	—7.28	—7.53
Change in cardiac index (l/min/m²)	—0.05	+0.02	+0.06	+0.30

*Urokinase pulmonary embolism trial.
**Urokinase-streptokinase pulmonary embolism trial.

Evaluations were obtained between 18 and 30 hours after the start of therapy. After several days, there were no differences between the results in the heparin treated patients and those receiving urokinase.

† Adapted from (7).

CONTRAINDICATIONS — Because thrombolytic therapy increases the risk of bleeding, urokinase is contraindicated in the following situations:

1. Surgery within ten days. Liver or kidney biopsy, lumbar puncture, thoracentesis or paracentesis, extensive or multiple cutdowns should be considered surgical procedures.
2. Intraarterial diagnostic procedure within ten days.
3. Ulcerative wound.
4. Recent trauma with possibility of internal injuries.
5. Visceral or intracranial malignancy.
6. Pregnancy and the first ten days of the post-partum period.
7. Ulcerative colitis, diverticulitis or an actively bleeding lesion (or one with a significant potential for bleeding) of the gastrointestinal or genitourinary tract.
8. Severe hypertension.
9. Acute or chronic hepatic or renal insufficiency.
10. Uncontrolled hypocoagulable state, including one that may be caused by a coagulation factor deficiency, thrombocytopenia, spontaneous fibrinolysis, or another purpuric or hemorrhagic disorder.
11. Chronic lung disease with cavitation, e.g., tuberculosis.
12. Subacute bacterial endocarditis or rheumatic valvular disease.
13. Recent cerebral embolism, thrombosis or hemorrhage. Treatment with urokinase is contraindicated for at least two months after cerebral embolism, thrombosis or hemorrhage because patients with cerebral infarction remain at risk of bleeding into the infarcted tissue.
14. Any other condition in which bleeding might constitute a significant hazard or be particularly difficult to manage because of its location.

The conditions listed above should not be regarded as absolute contraindications. Rather, the risk of hemorrhage must be weighed carefully against the anticipated benefits of urokinase therapy in an individual patient and the benefits and risks associated with the use of urokinase should be compared to the benefits and risks associated with other forms of therapy.

WARNINGS

Bleeding

Activation of the fibrinolytic system with urokinase results in a more profound alteration of the hemostatic status of the patient than does anticoagulant therapy with heparin or coumarin agents. The aim of urokinase therapy is the production of sufficient amounts of plasmin for the lysis of intravascular deposits of fibrin; however, fibrin deposits which provide hemostasis, for example, at sites of needle punctures, are also destined for lysis, and bleeding from such sites may occur. The possibility of bruising or hematoma formation, especially with intramuscular injections, is high during thrombolytic therapy. Unnecessary handling of the patient should be avoided. Strict attention should be given to this section and the CONTRAINDICATIONS section in order to minimize the risk of bleeding.

Because of the high risk of hematoma formation, intramuscular injections must be avoided during urokinase therapy, as with heparin therapy. Bleeding at sites of recent invasive procedures may occur. Hence, arterial invasive procedures must also be avoided before and during treatment with urokinase. Should an arterial puncture be *absolutely* necessary, the femoral artery must be avoided and the radial or brachial artery used. It should be done carefully by a physician experienced in such a procedure. Pressure should be applied for at least 15 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding. Also, venipunctures should be performed as carefully and infrequently as possible. If the bleeding from an invasive site is not serious, treatment may be continued with appropriate clinical observation. Local measures, i.e., pressure, should be initiated immediately.

Spontaneous bleeding from internal sites (not accessible for pressure application) may also occur. The risk of spontaneous bleeding is greater in patients with pre-existing hemostatic defects, eg., patients with histories suggestive of prior bleeding problems, with or without demonstrable abnormalities in platelet count, prothrombin time, partial thromboplastin time, or bleeding time. Such patients should be assessed carefully before initiating treatment with urokinase.

In addition to its fibrinolytic action, plasmin also degrades fibrinogen, Factor V, Factor VIII, and other proteins. The products of plasmin degradation of fibrinogen and fibrin (FDP/fdp) possess an anticoagulant effect. Bleeding may be difficult to control because of this anticoagulant effect.

Should serious spontaneous bleeding occur, the infusion of urokinase should be terminated immediately, and treatment instituted as described under ADVERSE REACTIONS.

Predispositon to Cerebral Embolism

Treatment with urokinase of patients with atrial fibrillation or other conditions in which there is possible risk of cerebral embolism may be hazardous because of the risk of bleeding into the infarcted area.

Use of Anticoagulants

Concurrent use of anticoagulants with urokinase is not recommended and may be hazardous. Before starting urokinase in patients being treated with heparin, the effects of heparin should be allowed to diminish with time. As a general rule, a thrombin time of *less than twice* the normal control value is adequate for starting urokinase infusions safely. Similarly, heparin should not be started following urokinase therapy until the thrombin time has returned to *less than twice* the normal control value.

Rethrombosis has been observed after termination of urokinase treatment. In order to minimize this risk, the use of intravenous heparin followed by oral anticoagulant therapy is considered a necessary adjunct following urokinase therapy (see DOSAGE AND ADMINISTRATION).

Use in Pregnancy

See CONTRAINDICATIONS.

Use in Children

Safety and effectiveness of urokinase therapy in children have not been established; therefore, treatment of such patients is not recommended.

PRECAUTIONS

Drug Interactions

Concurrent use of drugs that may alter platelet function, e.g., aspirin, indomethacin, and phenylbutazone, should be avoided. The interaction of ABBOKINASE (urokinase for injection) with other drugs has not been studied.

Laboratory Monitoring

In patients who have received heparin, the thrombin time should be measured prior to starting urokinase. (See WARNINGS.) Similarly, the thrombin time should be monitored following urokinase therapy prior to instituting heparin. (See DOSAGE AND ADMINISTRATION.) During urokinase administration, the levels of fibrinogen, plasminogen, Factor V, and Factor VIII are usually substantially diminished. Concomitantly, the level of fibrin(ogen) degradation products (FDP/fdp) is increased. The combination of reduced fibrinogen and increased FDP/fdp results in a prolongation of the thrombin time. While changes in any of these parameters may serve as confirmation of the existence of a lytic state, no adjustment of dosage should be made on the basis of these test results.

ADVERSE REACTIONS

Incidence and Management

Strict observance of the contraindications, warnings, and precautions to the use of urokinase is essential to minimize the incidence and severity of adverse effects.[7]

BLEEDING

Incidence

Where thrombolytic agents (streptokinase and urokinase) were used in the same controlled clinical trial, severe bleeding (patients receiving a transfusion of greater than two units of blood) was seen in 4 and 6%, respectively. Several fatalities due to cerebral hemorrhage have occurred during urokinase therapy.

Less severe spontaneous bleeding has been observed during urokinase treatment at approximately twice the frequency as that occurring during heparin therapy. Oozing of blood from sites of percutaneous trauma is frequent; hence, all invasive procedures, especially arterial punctures and intramuscular injections must be avoided and intravenous punctures kept to a minimum before and during treatment with urokinase.

A moderate decrease in hematocrit not accompanied by clinically detectable bleeding occurred in approximately one out of five patients treated with urokinase.

Management of Severe Bleeding

In case of serious bleeding, urokinase therapy must be discontinued. If blood loss has been large, packed red cells are indicated. Plasma volume expanders (other than Dextran) are indicated to replace blood volume deficit. If only whole blood is available, it may also be used. Although the use of aminocaproic acid (ACA, AMICAR®) in humans as an antidote for urokinase has not been documented, it may be considered if the hemorrhage is unresponsive to blood replacement. (See WARNINGS.)

ALLERGIC REACTIONS

Although urokinase is a protein of human origin, and *in vitro* tests with the drug, as well as intradermal test in humans, gave no evidence of induced antibody formation, the possibility of serious allergic reactions (including anaphylaxis) occurring with its use cannot be excluded. Relatively mild allergic reactions, e.g., bronchospasm and skin rash, were reported rarely.

FEVER

Febrile episodes occurred in approximately two to three out of 100 patients. A cause and effect relationship has not been established. Symptomatic treatment is usually sufficient to alleviate discomfort. The use of acetaminophen rather than aspirin is recommended.

DOSAGE AND ADMINISTRATION

Dosing

ABBOKINASE IS INTENDED FOR INTRAVENOUS INFUSION ONLY.

A priming dose of 2,000 I.U./lb (4,400 I.U./kg) of ABBOKINASE is given as the Abbokinase-Normal Saline admixture over a period of ten minutes. This is followed by a continuous infusion of 2,000 I.U./lb/hr (4,400 I.U./kg/hr) of ABBOKINASE (given as the Abbokinase-Normal Saline admixture) for 12 hours. The total volume of fluid administered should not exceed 200 ml.

Administer ABBOKINASE (urokinase for injection) by means of a constant infusion pump that is capable of delivering a total volume of 195 ml.

Anticoagulation After Terminating Urokinase Treatment

At the end of urokinase therapy, treatment with heparin by continuous intravenous infusion is recommended. Heparin treatment should not begin until the thrombin time has decreased to *less than twice* the normal control value. See manufacturer's prescribing information for proper use of heparin.

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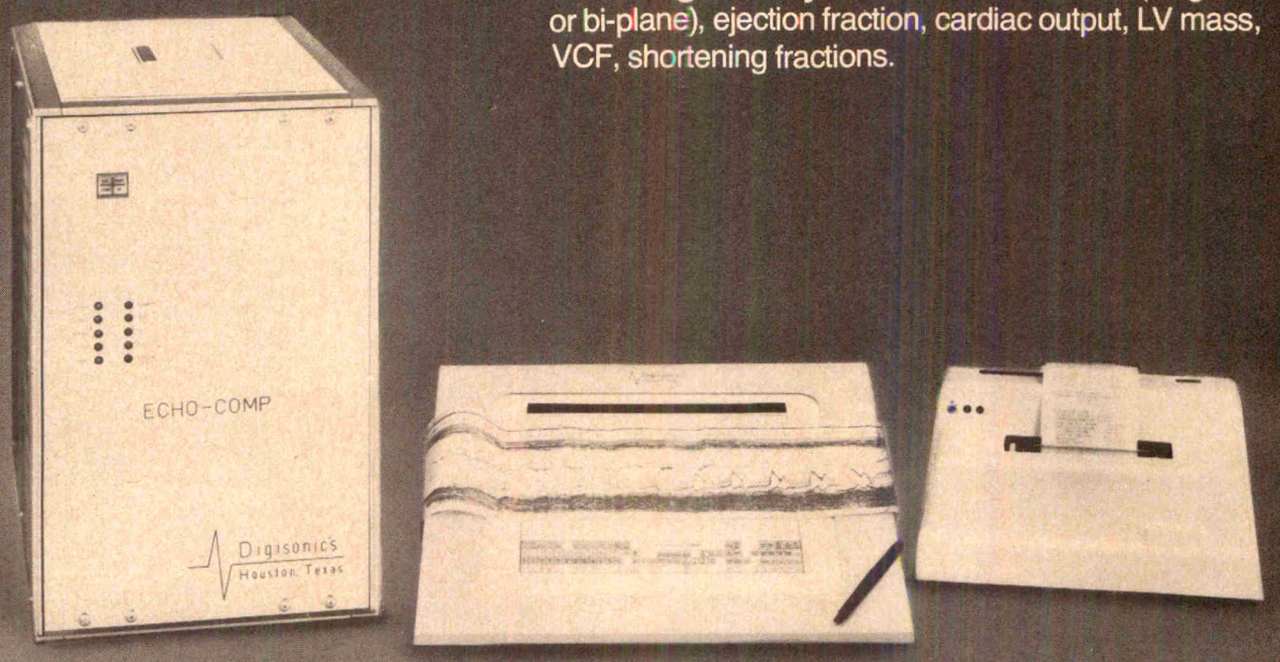
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DOSAGE AND ADMINISTRATION: Usual dose is 1-2 inches, as squeezed from tube. Some patients require 4-5 inches. To determine optimal dosage, start with 1 inch, increase dose 1/2 inch at a time until headache occurs, then drop back to largest dose which doesn't cause headache. Apply to desired skin area with Dose Measuring Applicator. DO NOT USE FINGERS. Spread in thin, uniform layer. May be applied every 3-4 hours if necessary. Effective in control of angina pectoris, regardless of skin site of application, although patients may prefer chest site because anginal pain originates in this area. To stop treatment of anginal patients, gradually reduce dosage and frequency of application over period of 4-6 weeks to prevent characteristic nitroglycerin withdrawal reactions.
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CAUTION: Federal law prohibits dispensing without prescription.

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REFERENCES: 1. Davidov ME, Mroczek WJ: The effect of nitroglycerin ointment on the exercise capacity in patients with angina pectoris.

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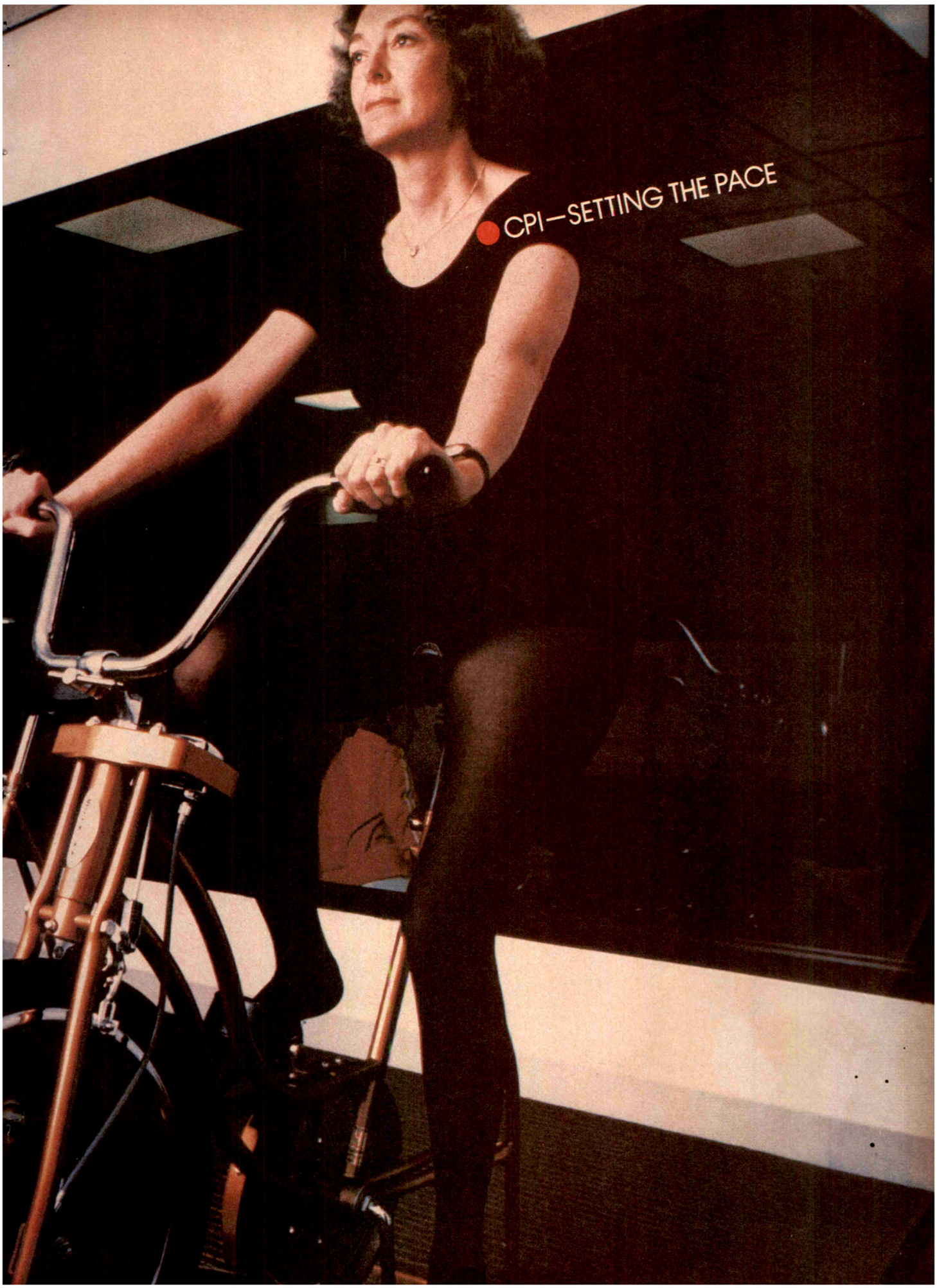
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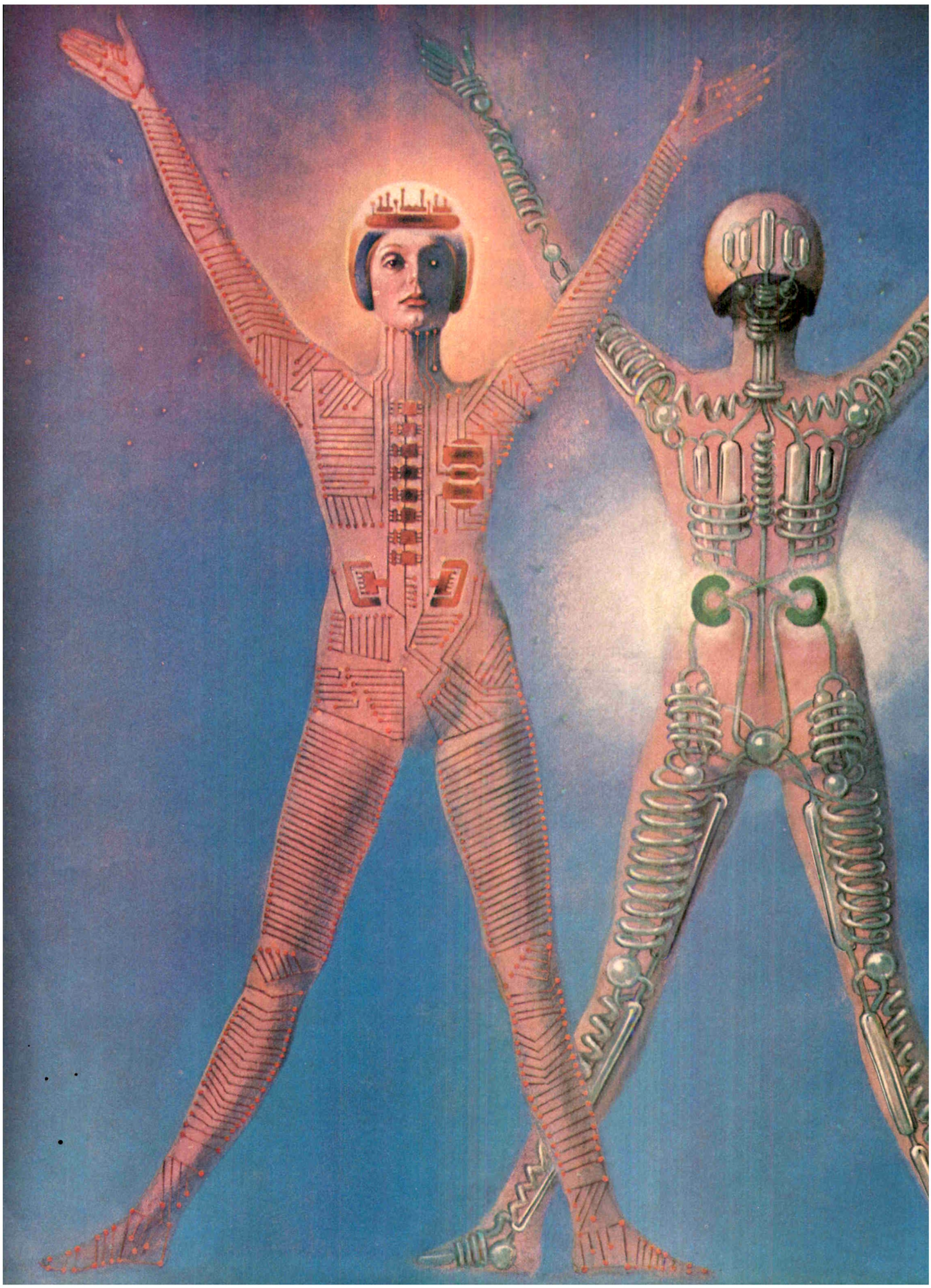


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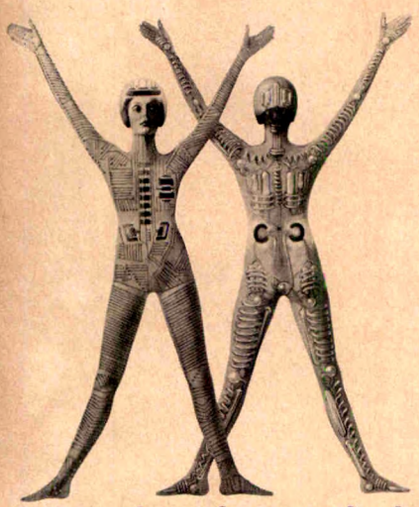



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in hypertension



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Warning: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Indication: The drug is indicated in the treatment of hypertension (see box warning).

Contraindications: Patients with known hypersensitivity to chlorthalidone and patients with severe renal or hepatic diseases.

Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine.

Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component.This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

A decreased glucose tolerance evidenced by hyperglycemia and glycosuria may develop inconsistently. This condition, usually reversible on discontinuation of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed should be checked regularly.

As with other diuretic agents hypokalemia may occur (see Precautions). Hyperuricemia may be observed on occasion and acute attacks of gout have been precipitated. In cases where prolonged and significant elevation of blood uric acid concentration is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Idiosyncratic drug reactions such as aplastic anemia, thrombocytopenia, leukopenia, agranulocytosis, and necrotizing angiitis have occurred, but are rare.

The remote possibility of pancreatitis should be considered when epigastric pain or unexplained gastrointestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reported with this general class of compounds include: jaundice, xanthopsia, paresthesia and photosensitization.

Overdosage: *Catapres (clonidine hydrochloride):* Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

How Supplied: Combipres® 0.1 (Each tablet contains clonidine hydrochloride 0.1 mg + chlorthalidone,15 mg). It is available as pink, oval, single-scored compressed tablets in bottles of 100.

Combipres® 0.2 (Each tablet contains clonidine hydrochloride 0.2 mg + chlorthalidone,15 mg). It is available as blue, oval, single-scored compressed tablets in bottles of 100.

For complete details, please see full prescribing information.

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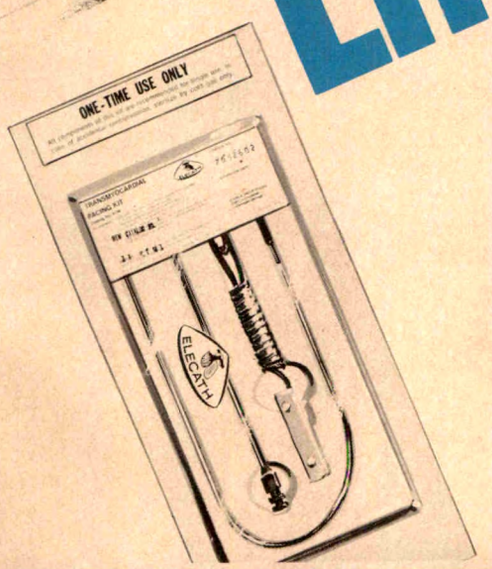
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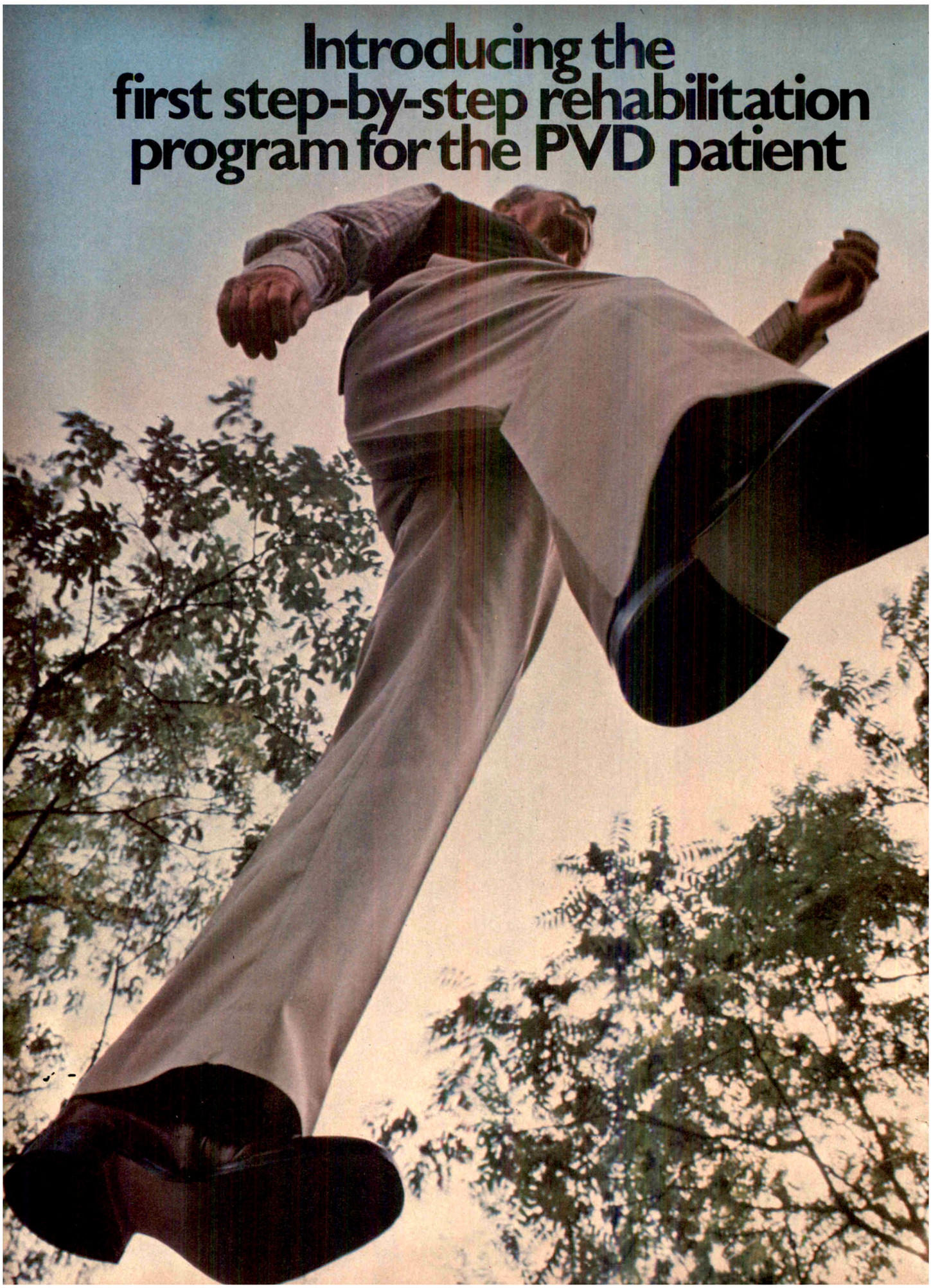


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You can receive this educational and instructional program by contacting your USV representative or by writing to: Walking Program, Medical Department, USV Laboratories Inc., Tuckahoe, N.Y. 10707.

The role of Arlidin (nylidrin HCl) in a walking program

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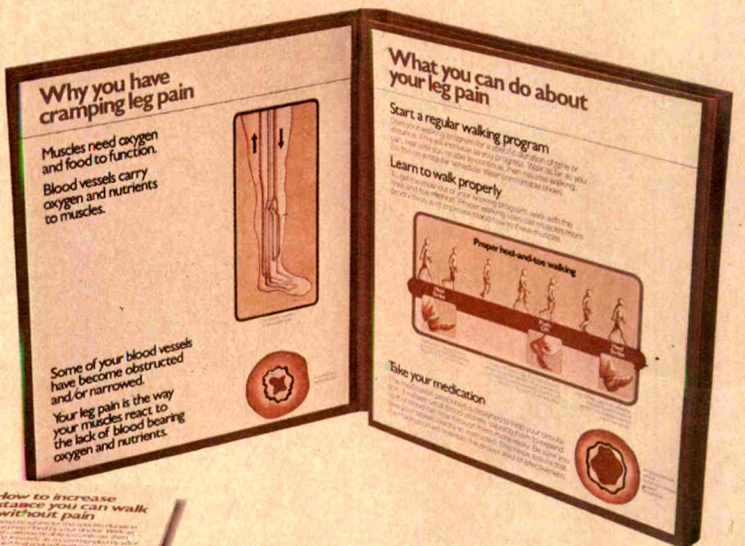
Relief of symptoms of ischemia associated with PVD*

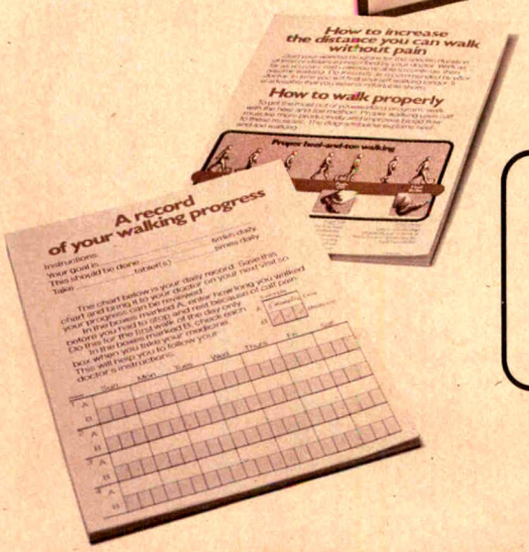
Symptomatic improvement can enhance the patient's ability to function and to comply with a recommended walking program.

Brief Summary

***Indications:** Based on a review of this drug by the National Academy of Sciences – National Research Council and/or other information, FDA has classified this drug as "possibly" effective for peripheral vascular disease and circulatory disturbances of the inner ear. Final classification of the less-than-effective indications requires further investigation.

Contraindications: Acute myocardial infarction, paroxysmal tachycardia, progressive angina pectoris and thyrotoxicosis. **Warnings:** In patients with cardiac disease such as tachyarrhythmias and uncompensated congestive heart failure, the benefit/risk ratio should be weighed prior to therapy and reconsidered at intervals during treatment. **Adverse Reactions:** Trembling, nervousness, weakness, dizziness (not associated with labyrinthine artery insufficiency), palpitations, nausea and vomiting may occur. Postural hypotension, while not reported, may also occur. **Dosage:** Orally, 3 to 12 mg. three or four times a day. **How Supplied:** White, scored tablets, 6 mg. and 12 mg. Bottles of 100 and 1000; single-dose blister packs, boxes of 100 (10 x 10 strips).



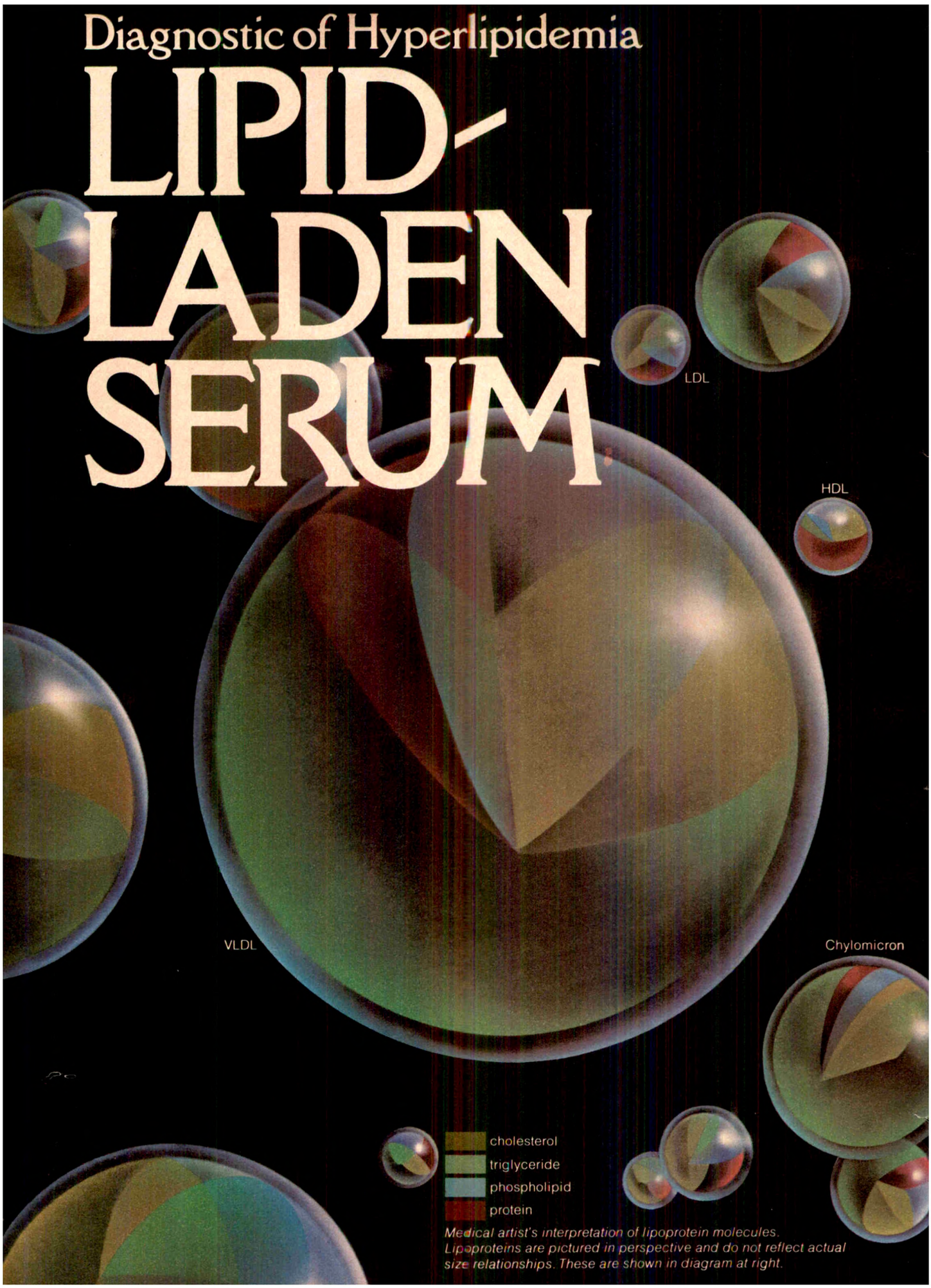


The rehabilitation program

Walking & Arlidin® (nylidrin HCl)

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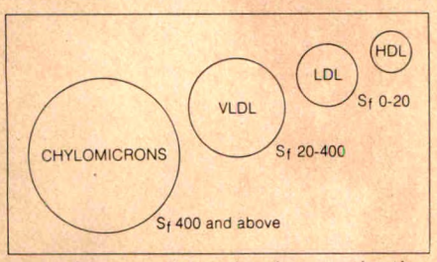
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Diagnostic of Hyperlipidemia
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Medical artist's interpretation of lipoprotein molecules. Lipoproteins are pictured in perspective and do not reflect actual size relationships. These are shown in diagram at right.

Lipoproteins: The "cargo" and the "transport vehicle"

Since fats are insoluble in water, they must link up with protein to remain dispersed in the blood. The lipoprotein molecules thus formed allow lipid substances—cholesterol, triglycerides, phospholipids—to travel freely in a soluble form through the bloodstream for use as structural building blocks and sources of energy. The four major classes of lipoprotein, consisting of varying amounts of lipids (the "cargo") and protein (the "transport vehicle") are chylomicrons, very low density lipoproteins (VLDL), low density lipoproteins (LDL), and high density lipoproteins (HDL). [See medical artist's interpretation at left.] The relative size of these lipoprotein molecules, based on measurement of flotation rates via ultracentrifugation, is shown below.

SCHEMATIC RELATION OF SIZE TO FLOTATION RATE (S_f)



Abnormalities in the production and/or degradation of these lipoproteins can lead to excessive accumulations of cholesterol and/or triglycerides in the serum. These elevations in serum lipids, in the absence of underlying causative disease, are diagnostic of hyperlipidemia.

Early intervention—a rational approach to the management of hyperlipidemia

Reducing elevated lipid levels is a rational therapeutic goal at any point in the hyperlipidemic process—but is perhaps most logical in the early stage. This is the stage when most patients are asymptomatic, yet routine cholesterol and triglyceride determinations will disclose that nevertheless they are hyperlipidemic.[1]

If persistent, clinically significant lipid elevations are demonstrated—and underlying disease states are ruled out through history, physical examination, and appropriate laboratory tests—a diagnosis of primary hyperlipidemia is confirmed.

Dietary modification directed at correcting the specific lipid abnormality should be instituted as the first therapeutic step, but it often fails to lower the lipids sufficiently.

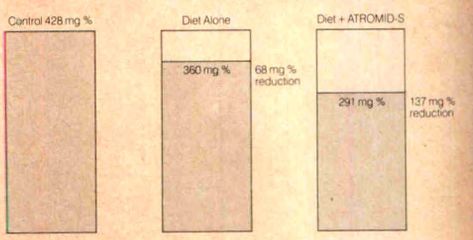
This is the best time to add ATROMID-S, an antilipidemic agent, to the regimen. Early, effective, and continuous lipid lowering is important in the successful management of hyperlipidemia.

When diet alone is not enough, Atromid-S can further reduce elevated serum lipids

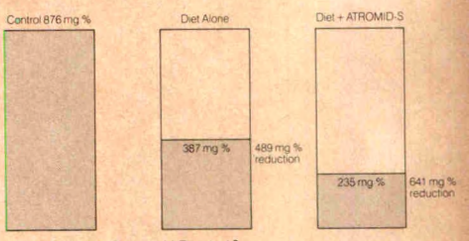
As an adjunct to diet and other measures, ATROMID-S depresses levels of both the very low density lipoproteins (S_f 20-400) and the low density lipoproteins (S_f 0-20), with an apparently greater effect on the former. The result of these actions is a reduction in elevated serum cholesterol (particularly the cholesterol carried by LDL) and/or triglycerides.

AN IMPORTANT NOTE: It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

ATROMID-S Lowers Cholesterol Significantly Better Than Diet Alone
Results in 7 patients with hypercholesterolemia
Mean Difference mg %*



ATROMIDS-S Lowers Triglycerides Significantly Better Than Diet Alone
Results in 7 patients with hypertriglyceridemia
Mean Difference mg %*



*Adapted from Brown, H.B., *et al.*[2]

Continuous therapy and constant dosage essential to long-term control

Lipid lowering is sustained as long as ATROMID-S treatment is uninterrupted. However, if the drug is stopped, lipid levels may return to or above pretreatment levels.

ATROMID-S is effective in a simple, well-accepted regimen. Initial *and* maintenance dosage is 2 g daily, in divided doses. Some patients may respond to a lower dosage.

IF GIVEN IN CONJUNCTION WITH ANTICOAGULANTS

WARNING: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

As an adjunct to diet

Atromid-S®

Brand of

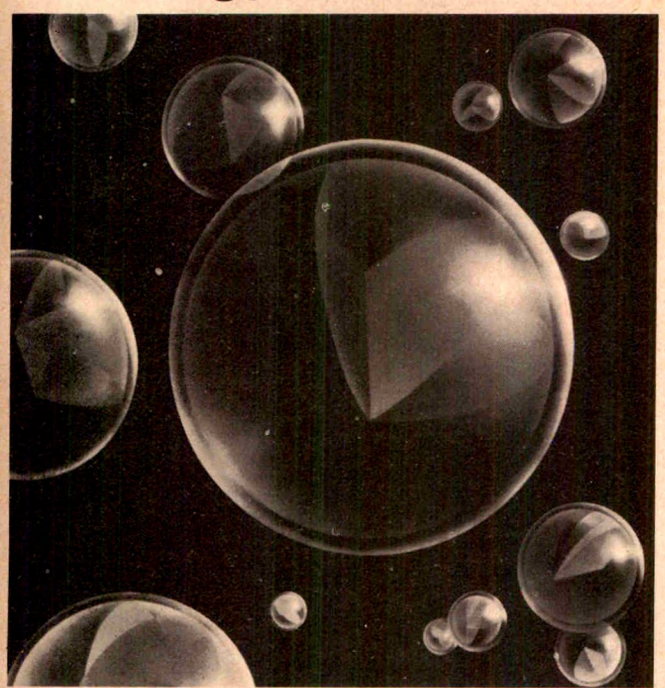
clofibrate

Helps reduce elevated serum levels of cholesterol and/or triglycerides

See last page of this advertisement for prescribing information.

Atromid-S® (clofibrate)

Helps reduce elevated serum levels of cholesterol and/or triglycerides



BRIEF SUMMARY

(For full prescribing information, see package circular.)

ATROMID-S® Brand of clofibrate

Antilipidemic agent for reduction of elevated serum lipids

INDICATIONS: ATROMID-S is indicated as adjunctive therapy in patients who do not respond adequately to diet and other measures for the reduction of elevated serum cholesterol (especially the beta lipoprotein fraction) and/or triglycerides. Clofibrate appears to have a greater depressant effect on the very low density lipoproteins (S_f 20-400) rich in triglycerides than the low density lipoproteins (S_f 0-20) rich in cholesterol.

ATROMID-S is also indicated for treatment of patients with xanthoma tuberosum associated with hyperlipidemia. The skin lesions frequently regress with clofibrate.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CONTRAINDICATIONS: Clofibrate is contraindicated in pregnant women. While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than that found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

It is contraindicated in lactating women since it is not known if clofibrate is secreted in the milk.

It is contraindicated in patients with clinically significant hepatic or renal dysfunction.

It is contraindicated in patients with primary biliary cirrhosis since it may raise the already elevated cholesterol in these cases.

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Strict birth control procedures must be exercised by women of childbearing potential. In patients who plan to become pregnant, clofibrate should be withdrawn several months before conception. Because of the possibility of pregnancy occurring despite birth control precautions in patients taking clofibrate, the possible benefits of the drug to the patient must be weighed against possible hazards to the fetus.

Administration of clofibrate to mice and rats in long-term studies at eight times the human dose resulted in a higher incidence of liver tumors than in controls. Lower doses were not studied. Although the relevance of this finding to humans is not known at this time, it cannot be dismissed especially since this drug is intended for long-term administration. ATROMID-S should be used only in patients with hyperlipidemia who do not respond adequately to dietary intervention.

PRECAUTIONS: Before instituting therapy with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.

Because of the long-term administration of a drug of this nature, adequate baseline studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be obtained during the first few months of ATROMID-S administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, the drug should be employed for longer periods (even up to one year) provided that there is a reduction in the size and/or number of the xanthomata.

Subsequent serum lipid determinations should be done to detect a paradoxical rise in serum cholesterol or triglyceride levels. Clofibrate will not alter the seasonal variations of serum cholesterol peak elevations in midwinter and late summer and decreases in fall and spring. If the drug is discontinued, the patient should be placed on an appropriate hypolipidemic diet, and his serum lipids should be monitored until stabilized, as a rise in these values to or above the original baseline may occur.

During clofibrate therapy, frequent serum transaminase determinations and other liver function tests should be performed since the drug may produce abnormalities in these parameters. These effects are usually reversible when the drug is discontinued. Hepatic biopsies are usually within normal limits. If the hepatic function tests steadily rise or show excessive abnormalities, the drug should be withdrawn. Therefore use with caution in those patients with a past history of jaundice or hepatic disease.

Clofibrate may produce "flu like" symptoms (muscular aching, soreness, cramping). The physician should differentiate this from actual viral and/or bacterial disease.

Use with caution in patients with peptic ulcer since reactivation has been reported. Whether this is drug-related is unknown.

Complete blood counts should be done periodically since anemia, and more frequently, leukopenia have been reported in patients who have been taking clofibrate.

Various cardiac arrhythmias have been reported with the use of clofibrate.

Several investigators have observed in their studies that clofibrate may produce a decrease in cholesterol linoleate but an increase in palmitoleate and oleate, the latter being considered atherogenic in experimental animals. The significance of this finding is unknown at this time.

ADVERSE REACTIONS: Of the pertinent reactions, the most common is nausea. Less frequently encountered gastrointestinal reactions are vomiting, loose stools, dyspepsia, flatulence, and abdominal distress. Reactions reported less often than gastrointestinal ones are headache, dizziness, and fatigue; muscle cramping, aching, and weakness; skin rash, urticaria, and pruritus; dry brittle hair, and alopecia.

The following reported adverse reactions are listed alphabetically by systems:

Cardiovascular
- Increased or decreased angina
- Cardiac arrhythmias
- Both swelling and phlebitis at site of xanthomas

Dermatologic
- Skin rash
- Alopecia
- Allergic reaction including urticaria
- Dry skin and dry brittle hair
- Pruritus

Gastrointestinal
- Nausea
- Diarrhea
- Gastrointestinal upset (bloating, flatulence, abdominal distress)
- Hepatomegaly (not associated with hepatotoxicity)
- Gallstones
- Vomiting
- Stomatitis and gastritis

Genitourinary
- Impotence and decreased libido
- Findings consistent with renal dysfunction as evidenced by dysuria, hematuria, proteinuria, decreased urine output. One patient's renal biopsy suggested "allergic reaction."

Hematologic
- Leukopenia
- Potentiation of anticoagulant effect
- Anemia
- Eosinophilia

Musculoskeletal
- Myalgia (muscle cramping, aching, weakness)
- "Flu like" symptoms
- Arthralgia

Neurologic
- Fatigue, weakness, drowsiness
- Dizziness
- Headache

Miscellaneous
- Weight gain
- Polyphagia

Laboratory Findings
- Abnormal liver function tests as evidenced by increased transaminase (SGOT and SGPT), BSP retention, and increased thymol turbidity
- Proteinuria
- Increased creatine phosphokinase

Reported adverse reactions whose direct relationship with the drug has not been established: peptic ulcer, gastrointestinal hemorrhage, rheumatoid arthritis, tremors, increased perspiration, systemic lupus erythematosus, blurred vision, gynecomastia, thrombocytopenic purpura.

DOSAGE AND ADMINISTRATION: *Initial:* The recommended dosage for adults is 2 g daily, in divided doses. Some patients may respond to a lower dosage.

Maintenance: Same as for initial dosage.

Note: In children, insufficient studies have been done to show safety and efficacy.

DRUG INTERACTIONS: Caution should be exercised when anticoagulants are given in conjunction with ATROMID-S. The dosage of the anticoagulant should be reduced usually by one-half (depending on the individual case) to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has been stabilized.

MANAGEMENT OF OVERDOSAGE: While there has been no reported case of overdosage, should it occur, symptomatic supportive measures should be taken.

HOW SUPPLIED: ATROMID-S—No. 243—Each capsule contains 500 mg clofibrate, in bottles of 100.

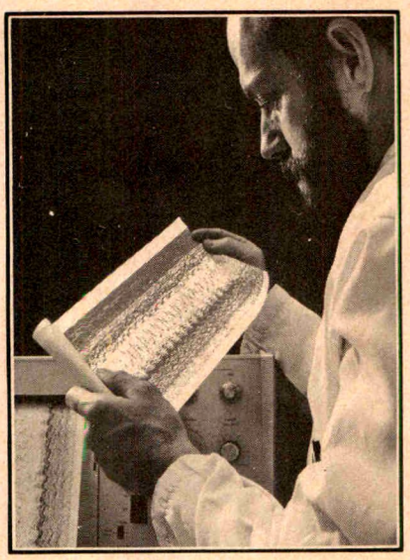
References: 1. Scheig, R.: Conn. Med. 39:71 (Feb.) 1975. **2.** Brown, H. B., Lewis, L. A., and Page, I. H.: Clin. Pharmacol. Ther. 17:171 (Feb.) 1975.

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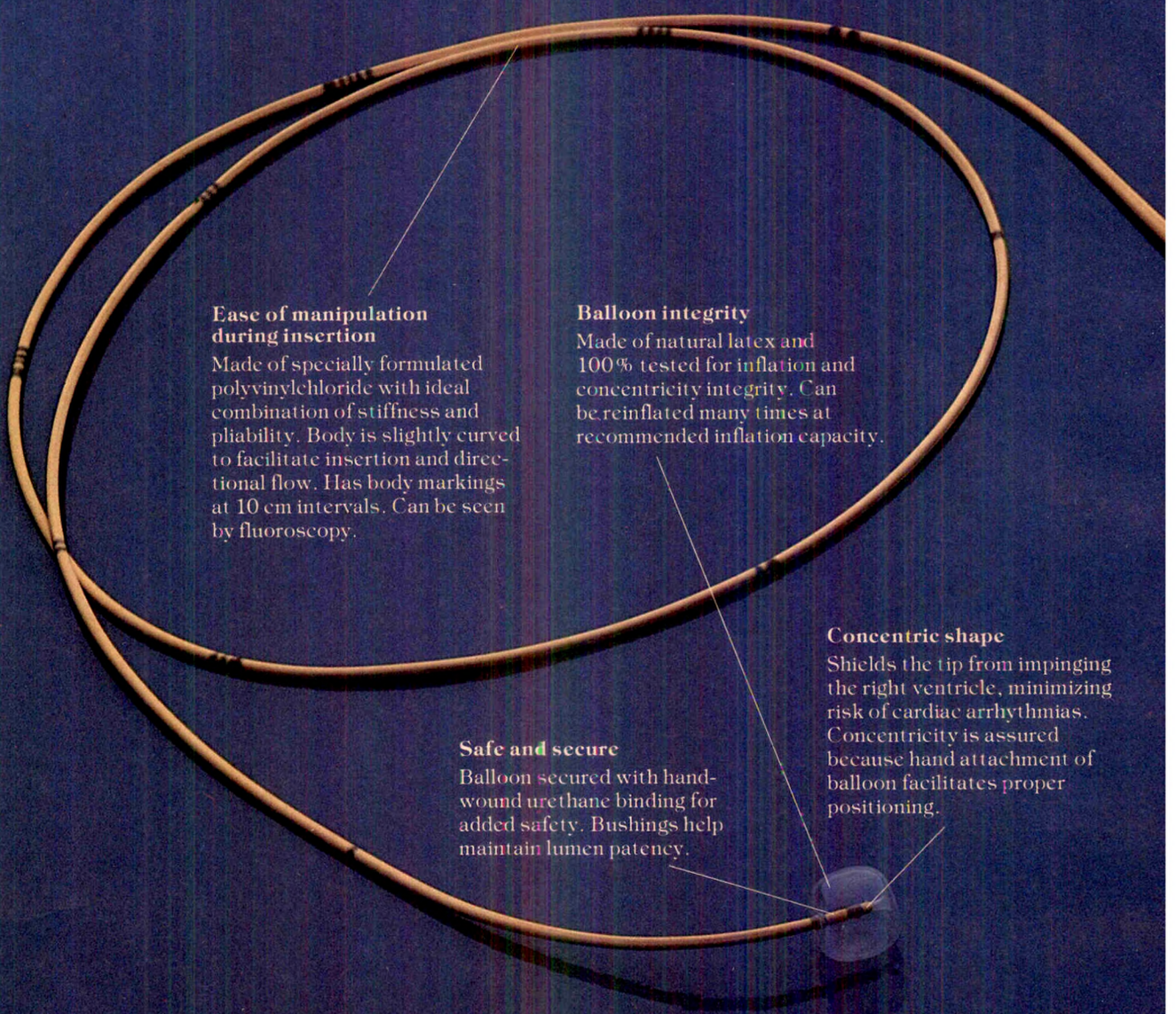
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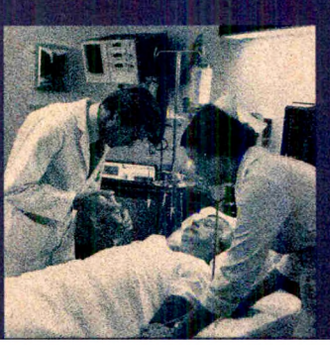
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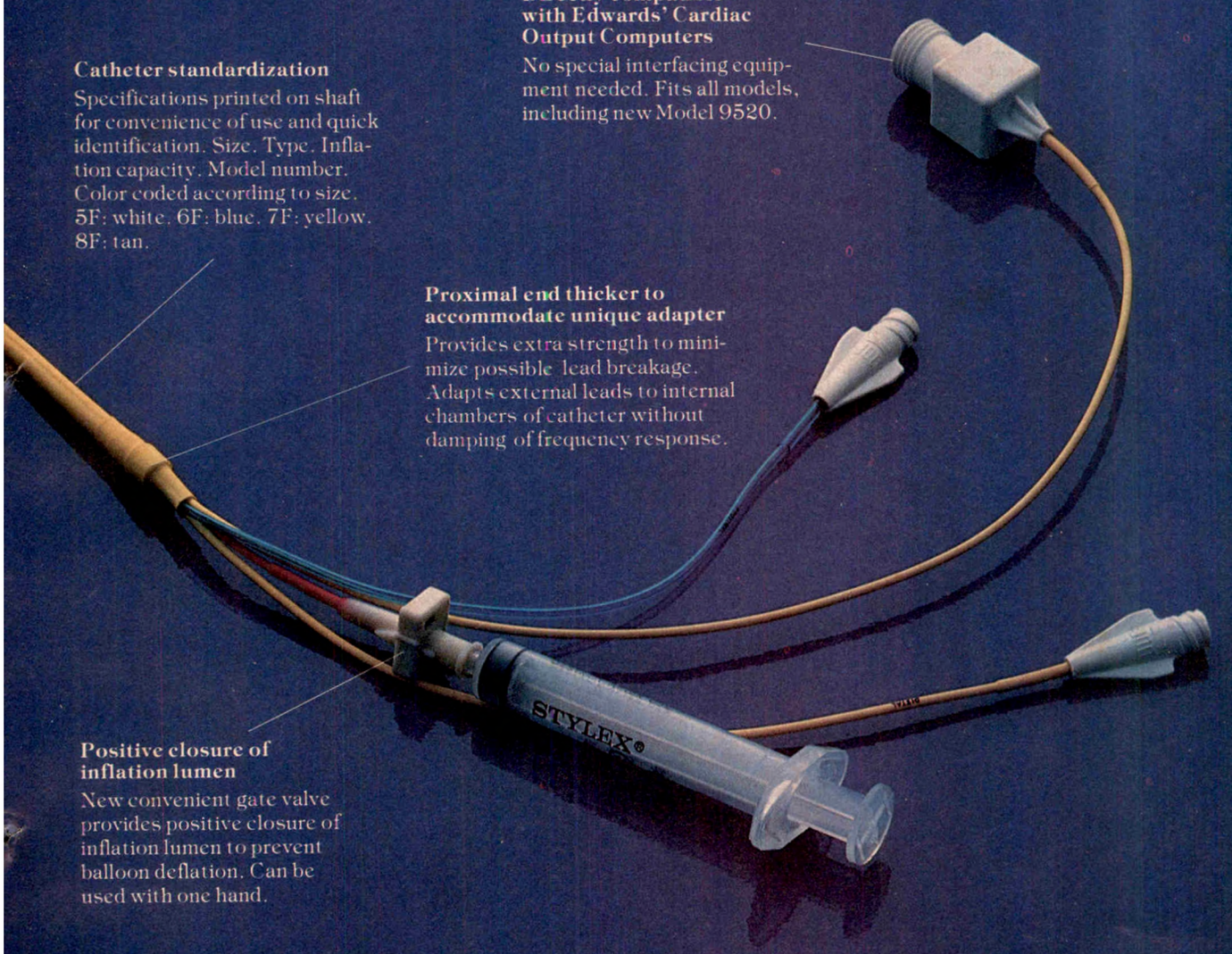


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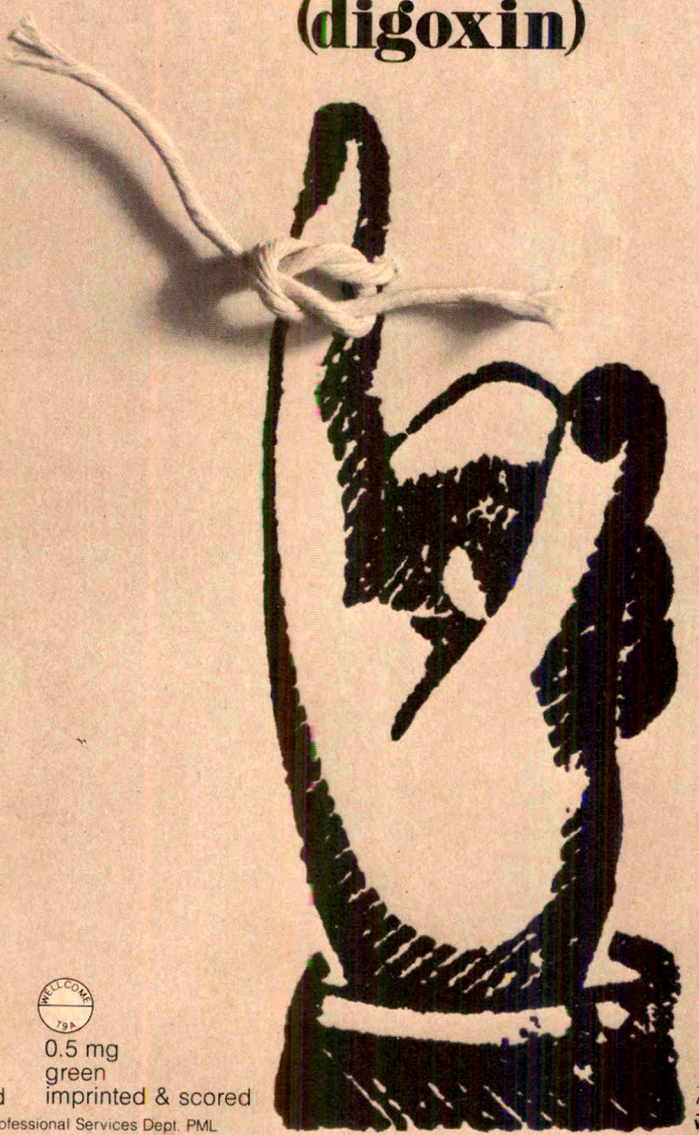
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VOLUME 41

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CLINICAL STUDIES

Ergonovine Maleate Provocative Test for Coronary Arterial Spasm

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Ergonovine maleate was evaluated as a provocative agent for inducing coronary spasm during coronary arteriography. The study group consisted of 98 patients with either mild fixed obstructions of coronary luminal diameter (less than 50 percent) or normal coronary arteriograms. The test was considered positive if the drug precipitated severe coronary spasm. A positive ergonovine test occurred in 10 of 11 patients with Prinzmetal's variant angina ($P < 0.02$). Two of these patients had a transmural myocardial infarction in the distribution of the spastic artery. Ergonovine tests were negative in (1) the 15 control patients with no clinically suspected coronary artery disease ($P < 0.001$), (2) 63 of 66 patients with angina-like chest pain ($P < 0.001$), and (3) all 6 patients with myocardial infarction and no history of Prinzmetal's variant angina ($P < 0.05$). No major complications occurred as a result of this test.

Thus, ergonovine maleate test is a safe, sensitive and specific method for reproducing coronary spasm in patients with Prinzmetal's variant angina and no major coronary obstructions. The results suggest that coronary spasm can be implicated as a cause of myocardial infarction in patients with normal coronary arteriograms who also have Prinzmetal's variant angina. Coronary spasm was not demonstrated in patients who had normal coronary arteriograms and a history of myocardial infarction as an isolated clinical event. Also, coronary spasm could not be demonstrated in the majority of patients who had angina-like chest pain and no major coronary obstruction.

Prinzmetal et al.[1] in 1959 described a variant form of angina pectoris that occurred repeatedly at rest in association with transient S-T segment elevation. They postulated that these attacks were precipitated by spasm superimposed on a fixed severe coronary obstruction. Gianelly et al.[2] in 1968 were the first to report a case of Prinzmetal's variant angina with no angiographically detectable severe coronary obstruction. Dhurandhar et al.[3] in 1972 angiographically demonstrated coronary spasm during angina in such a patient. Since then, numerous investigators have documented coronary spasm during Prinzmetal's variant angina in patients with no severe coronary obstruction.[4]

In December 1972, we initiated a prospective investigation of ergonovine maleate as a provocative agent for coronary spasm. This agent was first recommended by Stein[5] in 1949 for diagnosis of angina pectoris

From the Department of Cardiology, Cleveland Clinic Foundation, Cleveland, Ohio. Manuscript received August 3, 1977, revised manuscript received October 20, 1977, accepted October 26, 1977.

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TABLE I

Four Major Clinical Groups

Group	Clinical Characteristics
A (11 patients)	Prinzmetal's variant angina
B (15 patients)	Control subjects; no angina
C (66 patients	Angina-like chest pain
D (6 patients)	Myocardial infarction (without Prinzmetal's variant angina)

TABLE II

Clinical Findings in 11 Patients with Prinzmetal's Variant Angina and No Major Coronary Obstructions

Case no.	Age (yr) & Sex	Electrocardiogram: Pain-Free	Electrocardiogram: S-T Segment During Angina	Electrocardiogram: Arrhythmia During Angina
1				
Preop	55F	Normal	↑ II, III, aVF	Sinus arrest, A-V block, VT
Postop		Normal	Unknown	None (pacemaker functioning)
2				
Preop	50M	Normal	↑ II, III, aVF	VT
Postop		Normal	Unknown	None
3				
Preop	45F	Remote inferolateral MI	↑ II, III, aVF	2:1 A-V block, VT
4	47M	Normal	↑ aVF, III	Junctional rhythm
5	52M	Normal	↑ V_2–V_5	Sinus bradycardia, VT
6	49F	Normal	↑ II, III, aVF	VT
7	56F	Normal	↑ II, III, aVF	Sinus arrest, CHB, VF
8	24M	Normal	↑ aVL, I	None
9				
Preop	53F	Normal	↓ I, II, III, aVL, aVF	None
Postop		Normal	↑ V_1–V_4	VT
10	51F	Normal	↑ II, III, aVF	No
11	36F	Normal	↑ II, III, aVF	No

↓ = depression; ↑ = elevation; A-V = atrioventricular; CHB = complete heart block; MI = myocardial infarction; Postop = postoperative; Preop = preoperative; VF = ventricular fibrillation; VT = ventricular tachycardia.

This report describes our results in the first 98 patients evaluated with the ergonovine test at the Cleveland Clinic. This study was undertaken to evaluate (1) the sensitivity and specificity of ergonovine maleate as a provocative agent for coronary spasm by observing its effect in patients with Prinzmetal's variant angina and in control subjects, and (2) the ability of ergonovine maleate to precipitate coronary spasm in patients with angina-like chest pain or myocardial infarction who have no major coronary obstruction.

Methods

Patients: Ninety-eight patients underwent selective coronary arteriography, which revealed either normal arteries or fixed obstruction that narrowed the coronary luminal diameter by less than 50 percent. These patients were separated clinically into four groups (Table I). Patients with cerebrovascular disease were excluded. Informed consent was obtained from each patient before the test.

Group A consisted of 11 patients with Prinzmetal's variant angina (Table II), which we define as: (1) recurrent episodes of angina at rest; (2) transient S-T segment elevation during angina attacks (Fig. 1); and (3) normalization of the electrocardiogram between attacks, with no evidence of acute myocardial infarction.[4] This group included four men and seven women with an average age of 47 years. Transmural myocardial infarction developed in two patients, and variant angina continued after the infarction.

Group B, the control group, consisted of 15 patients in whom coronary disease was not suspected clinically. Ten had noncardiac chest pain, and 5 had cardiac valve disease or a minor electrocardiographic abnormality. This group included 12 men and 3 women with an average age of 36 years.

Group C was a clinically heterogeneous group of 66 patients with a history of angina-like chest pain but without Prinzmetal's variant angina. In three patients, the angina was typical, but in the remainder, it was considered atypical because of duration, quality or lack of relation to exertion. This group included 38 men and 28 women with an average age of 48 years.

Group D consisted of six patients with a previous myocardial infarction (inferior in four, anteroseptal in two) and no history of Prinzmetal's variant angina. New Q waves or loss of R wave amplitude developed in the electrocardiogram of all six patients during the acute infarction, and ventriculography demonstrated impaired contraction corresponding to the site of infarction indicated in the electrocardiogram. One patient continued to have typical angina after the infarction.

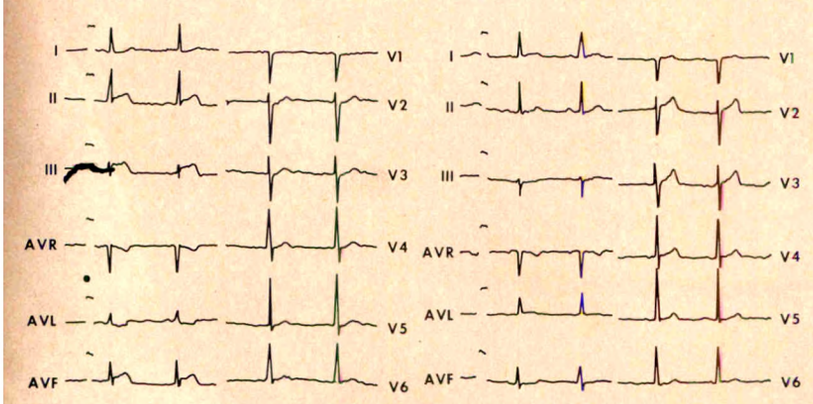


FIGURE 1. Patient 6, Group A (Prinzmetal's variant angina). Electrocardiograms demonstrating S-T segment elevation in inferior leads during Prinzmetal's variant angina **(left)** and return to normal after subsidence of angina **(right).**

This group included four men and two women with an average age of 42 years.

Catheterization protocol: After premedication with diazepam (Valium®) and an antibiotic agent, coronary arteriography was performed with the Sones technique[6] before and after administration of nitroglycerin. A left ventriculogram was then obtained. A temporary pacemaker was inserted in patients with syncope or bradyarrhythmias during angina. Ergonovine maleate, 0.1 mg, was administered as a bolus injection into the ascending aorta, usually between 15 and 45 minutes after administration of nitroglycerin. An electrocardiogram was recorded at 1 minute intervals. Intracardiac pressures were recorded before and 3 minutes after administration of the drug. Both coronary arteries were again visualized in multiple projections 5 minutes after injection of ergonovine maleate or earlier if angina or electrocardiographic changes occurred. If severe coronary spasm, angina or electrocardiographic changes did not develop within 10 minutes, 0.2 mg of ergonovine maleate was administered. The same angiographic procedure was then repeated. Sixteen patients with no coronary spasm after administration of 0.2 mg received 0.3 mg to evaluate dose-response relations. Because of limitations on the amount of contrast material injected, 50 patients received only the 0.2 mg dose.

If angina, major arrhythmia or hypotension developed, the ergonovine test was terminated, usually by administration of sublingual nitroglycerin, after both coronary arteries were visualized. In situations where more rapid vasodilatation was desired, nitroglycerin solution (0.4 mg/cc) was injected into the aorta or nitroprusside solution (50 mg/250 cc) was infused intravenously.

Analysis of angiographic response: The diameter of each coronary artery was measured at the site of the most severe narrowing after injection of ergonovine maleate. This value was compared with the normal diameter of the same artery before administration of nitroglycerin. The ergonovine test was considered positive if more than 75 percent narrowing developed within 10 minutes. The test was negative if less than 75 percent narrowing developed.

Statistical analysis: Within each of the four clinical groups, the hypothesis that negative and positive responses are equally likely was tested using a statistical analysis based on the normal approximation to the binomial distribution. The statistical comparison between Groups A and B was made with a standard chi-square test. For all tests, a continuity correction was made.

Results

The results are summarized in Table III and will be described separately for each group of patients. No fatal or disabling complications occurred as a result of the ergonovine test in any of the 98 patients. Arrhythmias developed in three patients in Group A and will be described in detail.

Group A: Ten of the 11 patients with variant angina (Table IV) had a positive ergonovine response ($P < 0.02$). One patient had a negative test even after administration of 0.3 mg. Eight of the 10 patients with a positive ergonovine test manifested angina and S-T elevation during the coronary spasm, one had angina without electrocardiographic changes and one had neither angina nor electrocardiographic changes. When present, angina or electrocardiographic changes occurred 3 to 6 minutes after administration of ergonovine.

Of the nine patients with variant angina who received 0.1 mg of ergonovine maleate, five had a positive response. Of the eight who received 0.2 mg, seven had a positive response (Fig. 2). Among those who received 0.1 mg initially, the minimal amount of ergonovine maleate necessary to produce coronary spasm ranged from 1.3 to 4.0 μg/kg (average 2.6).

Spontaneous coronary spasm with Prinzmetal's variant angina occurred during cardiac catheterization in Patients 2 and 3. Ergonovine maleate precipitated similar attacks of angina, identical electrocardiographic changes and coronary spasm in the same location. In Patients 5 and 7 severe coronary spasm without angina developed spontaneously. Ergonovine maleate produced more severe spasm in the same arteries in association with angina and electrocardiographic changes.

Severe spasm was observed in the right coronary artery in seven patients, left anterior descending artery

TABLE III

Summary of Ergonovine Responses

Ergonovine Response	Group A (Prinzmetal's angina)	Group B (control patients)	Group C (angina-like chest pain)	Group D (myocardial infarction)
Positive	10	0	3	0
Negative	1	15	63	6
Total	11	15	66	6
P value*	<0.02	<0.001	<0.001	<0.05

* *P* (probability) value calculated with chi square test.

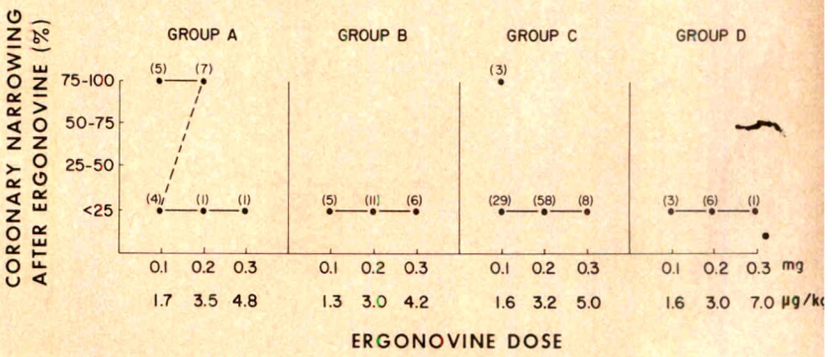


FIGURE 2. Dose-response relations for ergonovine maleate in each of four clinical groups (Group A, Prinzmetal's variant angina; Group B, control group; Group C, angina-like chest pain; Group D, prior myocardial infarction). Coronary arterial narrowing is expressed as a relation between the diameter of the most severely narrowed area after injection of ergonovine maleate compared with the same area before administration of nitroglycerin. The number of patients represented by each point on the curves is given in **parentheses.**

TABLE IV

Angiographic Findings in Group A

Case no.	Coronary Arteries After NTG	Spontaneous Coronary Spasm			Ergonovine Dose						Left Ventriculogram
					0.1 mg			0.2 mg			
		Angina	S-T Segment	Angio	Angina	S-T Segment	Angio	Angina	S-T Segment	Angio	
1											
Pre	20% RCA, & LAD				No	No change	30% RCA	Yes	↑ II, III, aVF	95% RCA, 50% LAD, 50% LCx	Normal
Post	100% RCA, 20% LAD				No	No change	40% LAD & RCA				Normal
2											
Pre	20% LCx, 10% RCA	Yes	↑ II, III, aVF	100% RCA	No	No change	Same	Yes	↑ II, III, aVF	100% RCA	Normal
Post	100% RCA, 20% LCx							Yes	No change	80% LAD, 60% LCx	
3											
Pre	10% RCA, 20% LAD	Yes	↑ II, III, aVF; 2:1 A-V block, VT	95% RCA				Yes	↑ II, III, aVF; 2:1 A-V block, PVC's	100% RCA, 80% LCx	Inferior akinesia
4											
	20% RCA & LAD				No	No change	95% RCA, 50% LAD & LCx				Normal
5											
	10% LAD	No	No change	80% LAD	No	No change	80% LAD	Yes	↑ V_2	95% LAD, 50% LCx	Normal
6											
	10% RCA				No	No change	30% RCA	Yes	↑ II, III, aVF; VT	100% RCA	Mitral valve prolapse
7											
	10% RCA	No	No change	90% RCA, LAD, LCx				Yes	↑ II, III, aVF; severe sinus bradycardia	100% RCA, 90% LAD & LCx	Normal
8											
	40% LAD				No	No change	Same	No	No change	Same	
9											
Pre	10% LAD, 80% LMT (spasm)	No	II; hypotension, VT	80% LMT, 95% LAD							Normal
Post	10% LAD, LMT				Yes	↑ aVL, V_2	100% LAD & LCx				Normal
10											
	10% LAD	Yes	No change	80% LCx	Yes	No change	80% LCx	Yes	No change	90% LCx, 50% LAD	Normal
11											
	10% RCA				Yes	↑ II, III, aVF	100% RCA			Normal	

↓ = depression; ↑ = elevation; Angio = angiographic findings; A-V = atrioventricular; LAD = left anterior descending; LCx = left circumflex; LMT = left main trunk; NTG = nitroglycerin; Post = postoperative; Pre = preoperative; PVC's = premature ventricular contractions; RCA = right coronary artery; VT = ventricular tachycardia.

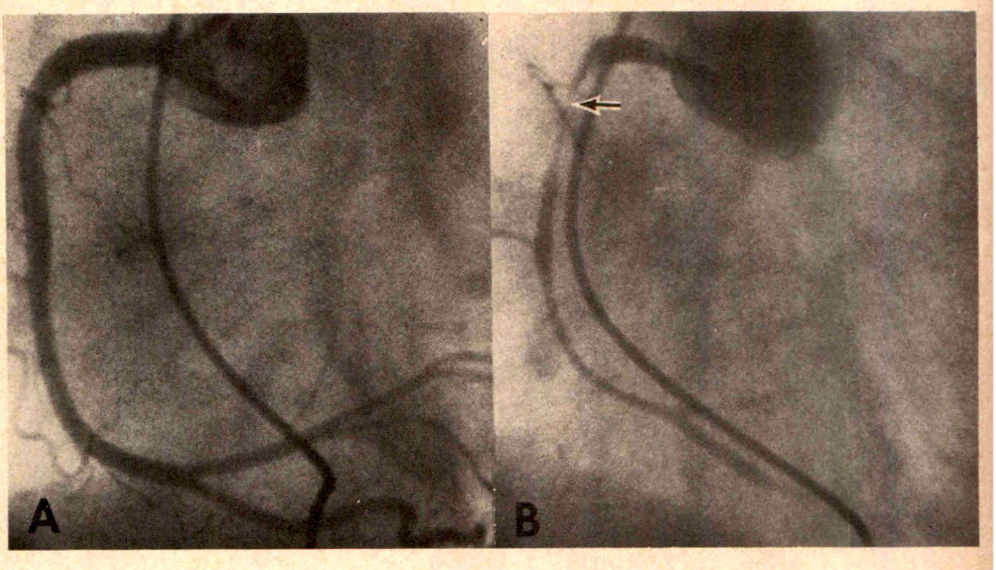


FIGURE 3. Patient 1, Group A. Arteriograms of right coronary artery in left anterior oblique projection. **A,** dilated coronary artery after nitroglycerin. **B,** subtotal obstruction **(arrow)** in proximal one third after ergonovine maleate. The patient experienced angina and had S-T segment elevation in the inferior leads at this time.

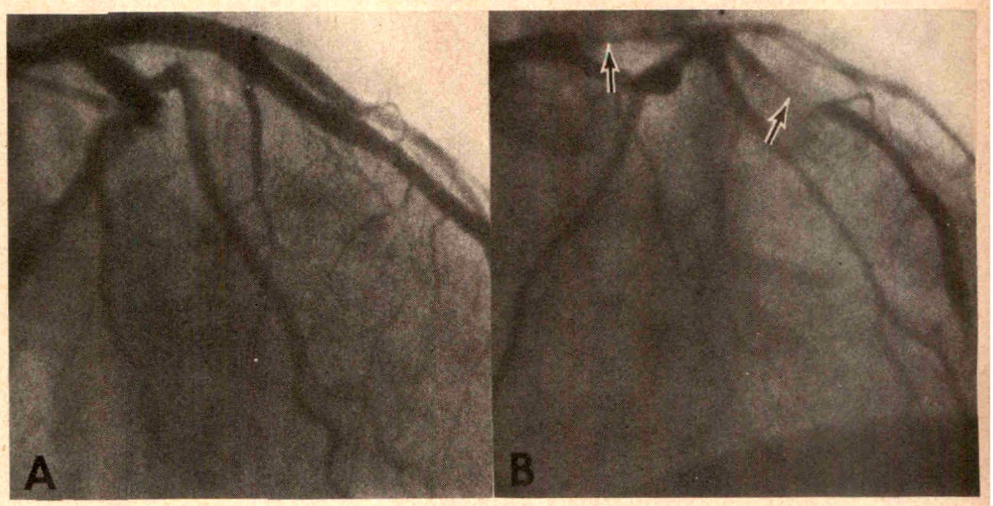


FIGURE 4. Patient 5, Group A. Arteriograms of left coronary artery in right anterior oblique projection. **A,** after nitroglycerin, the Sones catheter could be passed into the dilated left anterior descending coronary artery to the level of the first septal perforating branch without damping of pressure. **B,** after ergonovine maleate, two areas of severe spasm **(arrows)** developed in the proximal left anterior descending artery in association with angina and S-T segment elevation in precordial leads.

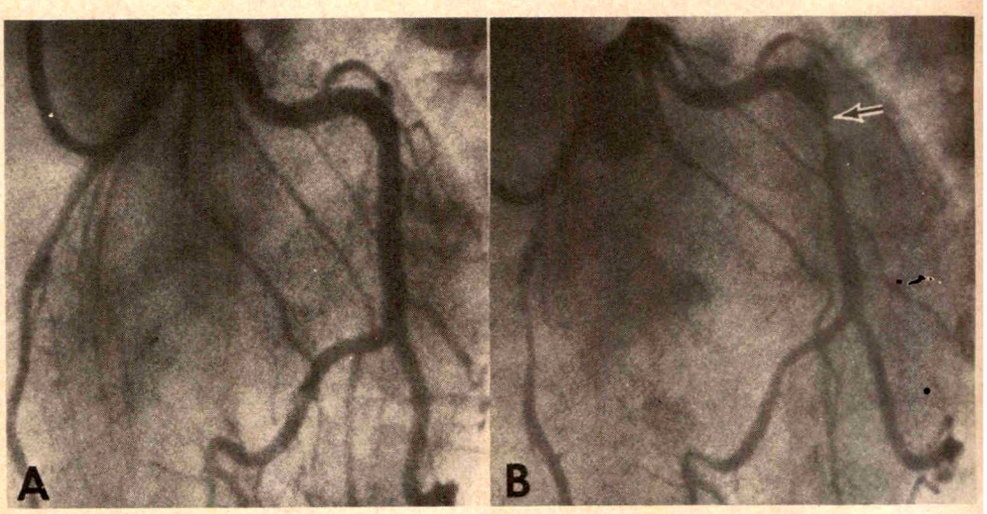


FIGURE 5. Patient 10, Group A. Arteriograms of left coronary artery in left anterior oblique projection. **A,** after nitroglycerin, only trivial irregularities can be detected. **B,** after ergonovine maleate, a localized 90 percent obstruction **(arrow)** occurred in the circumflex coronary artery. During spasm, the patient had angina but no electrocardiographic changes.

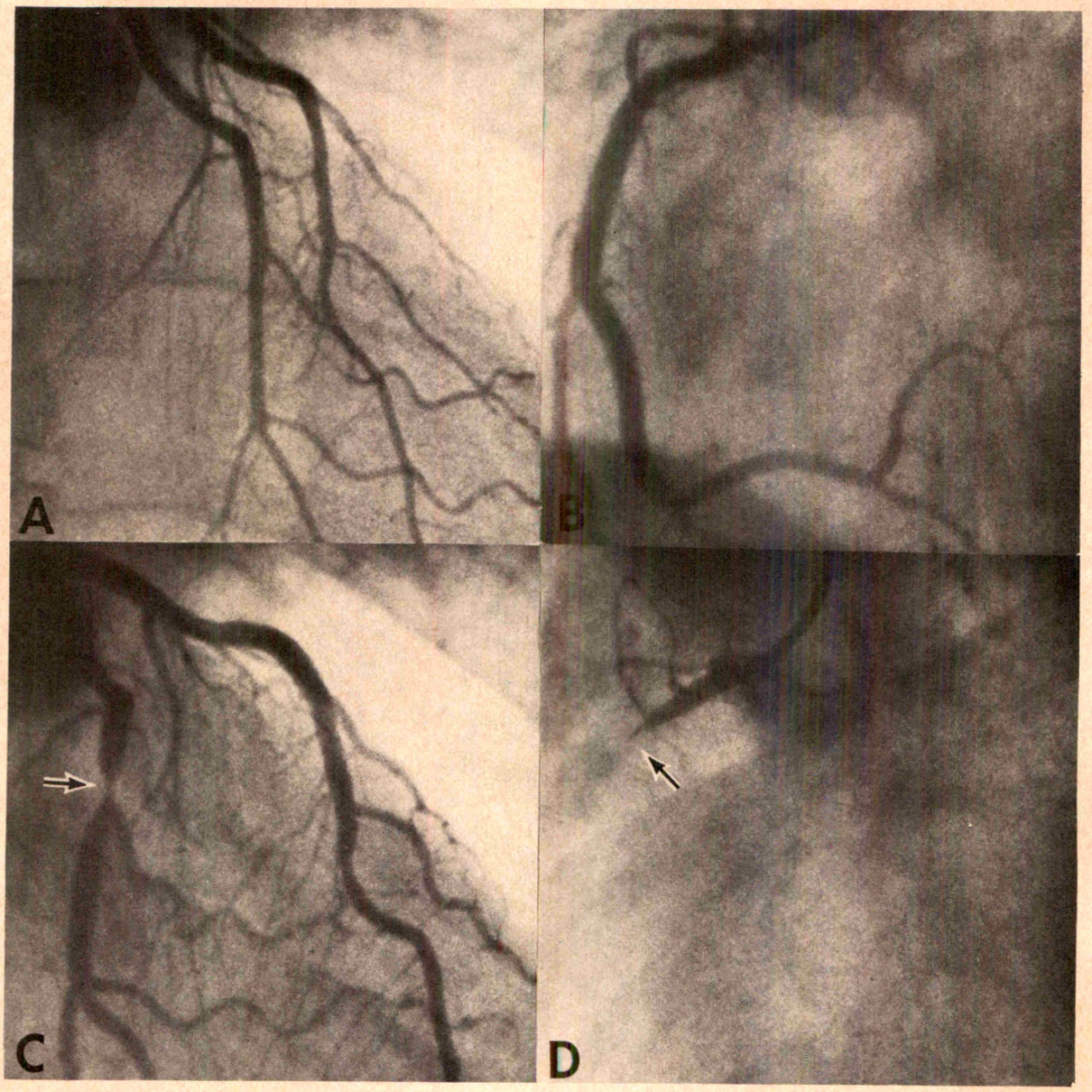


FIGURE 6, A to D. Patient 3, Group A. Arteriograms of left coronary artery in right anterior oblique projection **(A)** and right coronary artery in left anterior oblique projection **(B)** appear nearly normal after nitroglycerin. **C,** localized 80 percent obstruction **(arrow)** occurred in the circumflex artery **(C),** and total obstruction **(arrow)** occurred in the proximal right coronary artery **(D)** after ergonovine maleate. Angina, S-T segment elevation in the inferior leads and 2:1 atrioventricular block developed during spasm.

in four, circumflex artery in four and left main trunk in one (Fig. 3 to 5). Four patients had severe spasm in more than one coronary artery. In four patients coronary spasm varied in location from one segment of the artery to another with subsequent injections. In five patients spasm was limited to the proximal coronary artery, and in four it occurred throughout the artery.

Patient 3 had had an acute transmural inferolateral myocardial infarction 4 years before cardiac catheterization. The left ventriculogram demonstrated inferior wall akinesia. Ergonovine maleate precipitated transient total obstruction of the right coronary artery and 80 percent obstruction of the circumflex artery, with S-T segment elevation in the inferior leads (Fig. 6). Patient 1 had an inferior myocardial infarction 10 months after her last catheterization.

Arrhythmias occurring after administration of ergonovine maleate were similar to those recorded during spontaneous attacks of variant angina. Patient 6 had short runs of ventricular tachycardia during ergonovine-induced angina. This patient responded promptly to a bolus injection of intravenous lidocaine and sublingual nitroglycerin. Patients 3 and 7 underwent pacing with a transvenous pacemaker because of bradyarrhythmias that occurred during ergonovine-induced angina. No patient required defibrillation.

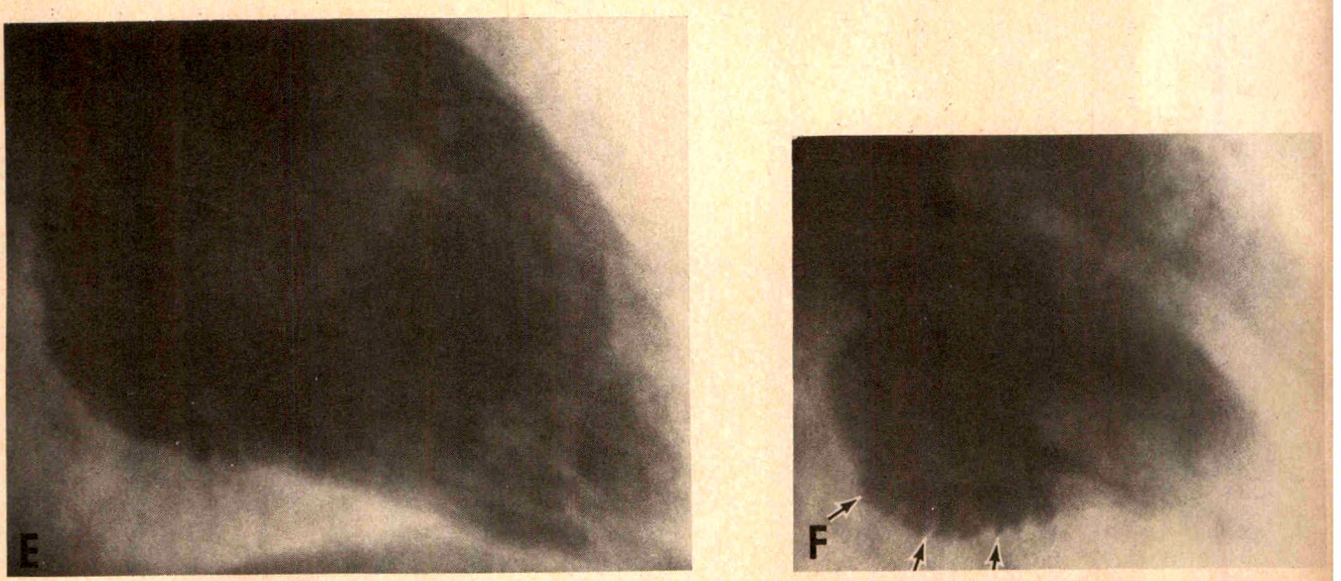


FIGURE 6, E and F. The left ventriculogram in diastole **(E)** and systole **(F)** demonstrates an akinetic area **(arrows)** in the proximal diaphragmatic wall in the distribution of the right coronary artery. The ventriculogram was performed before the ergonovine test. The area of akinesia corresponds to the remote inferior wall infarction indicated in the electrocardiogram.

The average changes in systolic blood pressure 3 minutes after administration of 0.1 and 0.2 mg of ergonovine maleate were +11 and +2 mm Hg, respectively. At the onset of angina, hypotension developed in three patients, with systolic blood pressure of less than 90 mm Hg.

Coronary spasm induced by ergonovine maleate was reversed within 3 minutes by one or two nitroglycerin tablets in 10 patients. Intravenous infusion of sodium nitroprusside abolished coronary spasm and angina within 1 minute in two patients, and intracoronary injection of nitroglycerin solution had a similar effect in one patient.

Patients 1, 2 and 3 received aortocoronary saphenous vein grafts to the right coronary artery only after all attempts at medical management were unsuccessful. In each patient, the segment of the artery that demonstrated spasm was resected, the artery was ligated at this level and the saphenous vein graft was inserted distally. Patient 9, with spasm of the left main trunk, had a double bypass to the anterior descending and circumflex coronary arteries for intractable angina. No coronary arterial resection or ligation was performed in this patient.

Group B: Each patient in the control group had a negative ergonovine test. This response is significantly different from the response in Group A ($P < 0.001$). All received at least 0.2 mg of ergonovine maleate (Fig. 2). Ten of the 15 patients had normal coronary arteries, and 5 had mild obstructions of up to 30 percent. Average changes in systolic blood pressure after 0.1, 0.2, and 0.3 mg of ergonovine maleate were +7, +9 and +10 mm Hg, respectively.

Group C: The ergonovine maleate test was negative in 63 and positive in 3 of the 66 patients with angina-like chest pain ($P < 0.001$). Each of the three patients with a positive test had a distinctive clinical syndrome.

The first of these three patients had a history of repeated episodes of nocturnal angina that were promptly relieved with nitroglycerin. An electrocardiogram was never obtained during these episodes. The second patient experienced repeated attacks of angina with exertion and at rest in association with S-T segment depression. Ergonovine produced coronary spasm, angina and similar electrocardiographic changes. The third patient had prolonged chest pain only once, after a double dose of ergotamine tartrate for a migraine headache. An electrocardiogram at that time demonstrated transient T wave abnormalities.

Forty-two patients had normal coronary arteriograms, and 24 had mild (less than 50 percent) obstruction. Seven patients had "catheter-induced" coronary spasm before administration of ergonovine maleate. The ergonovine response was negative in all seven. The average increase in systolic blood pressure after each dose of ergonovine maleate was 6 mm Hg.

Group D: Six patients had a remote myocardial infarction without a history of Prinzmetal's variant angina. The ergonovine response was negative in all of these patients ($P < 0.005$).

Discussion

The purpose of this study was to evaluate ergonovine maleate as a provocative agent for inducing coronary spasm during coronary arteriography. We verified that coronary artery spasm, in the absence of a severe fixed obstruction, can precipitate Prinzmetal's variant angina.[7–21] Because spontaneous coronary spasm with variant angina during coronary angiography is a fortuitous event, a provocative agent offers the advantage of

providing a prompt diagnosis. Without angiographic documentation, the diagnosis of clinically important coronary spasm can only be suspected.

The ergonovine test in Prinzmetal's variant angina: Our data demonstrate that ergonovine maleate is useful for provoking coronary spasm in patients with Prinzmetal's variant angina and no major coronary obstruction. Because 10 of the 11 patients with this syndrome had a positive test, it appears that ergonovine maleate has an acceptable level of sensitivity for reproducing coronary spasm in these patients. In addition, it produces coronary spasm and electrocardiographic changes identical to those that occur spontaneously. It is not apparent why one patient with the Prinzmetal syndrome had a negative ergonovine test. It may be that the test lacks sufficient sensitivity or that a different pathophysiologic mechanism produced the syndrome. Since December 1972, when we introduced the ergonovine maleate test for coronary spasm, other investigators[22–28] have reported similar experiences with this test.

Methacholine has also been used as a provocative agent for coronary spasm. Endo et al.[11] and Stang et al.[29] provoked coronary spasm and Prinzmetal's variant angina with this drug in small groups of patients. However, Yasue et al.[30] were able to provoke coronary spasm with methacholine in only 3 of 10 patients with Prinzmetal's variant angina and normal coronary arteriograms. At present not enough evidence is available regarding the sensitivity and specificity of methacholine to compare it with ergonovine maleate.

Technical aspects of the ergonovine test: Ergot alkaloids produce vasoconstriction by direct action on vascular musculature. In addition, they produce stimulation or depression of various centers in the central nervous system. Ergonovine maleate (Ergotrate®) is a weak vasoconstrictor, used primarily as an oxytocic agent.[31] It should not be confused with the strong vasoconstrictor ergotamine tartrate (Gynergen®), used for treatment of migraine headaches.

We attempted to establish the optimal dose of ergonovine maleate by constructing dose-response curves. Spasm did not develop in some patients after 0.1 mg, but did after 0.2 mg; thus, the test should not be considered negative unless this larger dose is given. Patients weighing more than 90 kg may require 0.3 mg because the average minimal dose necessary to produce coronary spasm was nearly 3 μg/kg. Because the duration of action of ergonovine maleate on coronary smooth muscle is unknown, it is possible that a cumulative effect of repeated injections occurred. However, this effect could not account for the difference in response between patients with a positive and a negative ergonovine test because the average cumulative dose of ergonovine was much greater in the patients with a negative ergonovine test.

Two patients in Group A (Patients 2 and 3) had spontaneous coronary spasm and variant angina before administration of nitroglycerin. In both, coronary spasm was not observed during previous coronary arteriograms obtained after nitroglycerin was administered. This suggests that premedication with vasodilators may mask spontaneous coronary spasm during angiography. Other investigators[32] have reported this masking effect with atropine, as well. We recommend that coronary arteriography be performed before administration of nitroglycerin or atropine when coronary spasm is suspected.

Because Prinzmetal's variant angina and major arrhythmias may occur during coronary spasm, the ergovonine maleate test should be performed under the supervision of a cardiologist in a catheterization laboratory. It should not be used as a bedside diagnostic maneuver. Because it may be necessary to perform rapid alternate visualization of the right and left coronary arteries during coronary spasm, the Sones technique is preferred.

The ergonovine test in control patients: The effects of ergonovine maleate were evaluated in patients with no clinical evidence of coronary artery disease to determine the normal response to ergonovine maleate. In the control patients (Group B), ergonovine maleate produced no more than 30 percent narrowing compared with the caliber before nitroglycerin was given. The difference in response between patients in Groups A and B confirms the specificity of ergonovine maleate.

The ergonovine test in angina-like chest pain: The etiology of angina-like chest pain in many patients with normal coronary arteriograms is unknown. The chest pain in such patients may arise from the gastrointestinal tract or musculoskeletal system of the chest wall. Other possible explanations include obstructions missed on coronary arteriography, small vessel disease, hemoglobin-oxygen dissociation abnormalities and coronary spasm.[33,34] Coronary spasm could not be precipitated by ergonovine maleate in 63 of 66 such patients in this study. A negative ergonovine test does not necessarily exclude coronary spasm as a possible cause of chest pain in some of these patients because different pathophysiologic mechanisms may be operating to produce coronary spasm.

Each of the three patients in this group who had a positive ergonovine test had a distinctive clinical syndrome. The first patient may have had the Prinzmetal syndrome because his episodes of angina occurred only during sleep. Unfortunately, an electrocardiogram was never obtained during one of these episodes. The second patient had spasm-induced angina with S-T segment depression. The third patient demonstrates that symptomatic coronary spasm may occur only when precipitated by a vasoconstrictor.

The ergonovine test in patients with "catheter-induced" coronary spasm: For years, coronary angiographers have recognized a benign form of coronary spasm, often called "catheter-induced" spasm.[35,36] This occurs in 1 to 3 percent of all coronary angiograms, usually in the proximal right coronary artery and in a localized segment near the catheter tip.[8,14,20,35,36] It does not produce angina, electrocardiographic abnormalities or hypotension, and it is of no known clinical significance. It is not apparent why catheter-induced spasm, even when severe, does not produce signs of myocardial

ischemia. It is possible that the duration and severity of spasm and changes in arteriolar resistance all play a part in producing myocardial ischemia.

Of the seven patients with catheter-induced coronary spasm, none manifested coronary spasm after ergonovine maleate. This finding suggests that the spasm occurring in these patients has different pathophysiologic features from those in Prinzmetal's variant angina. In the absence of a provocative agent such as ergonovine maleate, the occurrence of coronary spasm without angina or ischemic electrocardiographic changes in a patient with a history of angina-like chest pain is not sufficient reason to attribute the patient's symptoms to the spasm, even if the spasm is severe.

The ergonovine test in myocardial infarction with no major coronary obstruction: Coronary spasm has been postulated as a cause of myocardial infarction in patients with no severe fixed coronary obstruction.[37–39] Coronary spasm could not be induced by ergonovine maleate in six such patients in this study. The negative ergonovine test in these patients does not necessarily exclude coronary spasm as a cause of myocardial infarction since the pathophysiologic mechanism in operation at the time the infarction occurred may not have been present at the time of catheterization. In this series, the only patients with myocardial infarction in whom coronary spasm could be demonstrated were two patients who also had Prinzmetal's variant angina (Patients 1 and 3).

Present status of the ergonovine test: The ergonovine maleate test can be used to confirm coronary spasm in most patients with Prinzmetal's variant angina and no major coronary obstruction. It can be helpful in evaluating patients with normal coronary arteriograms and angina at rest in whom it has been impossible to obtain an electrocardiogram during pain. A positive ergonovine test in such patients is strong evidence in favor of coronary spasm as the cause of the symptoms, and a negative test is suggestive evidence that the chest pains are not due to coronary spasm. Finally, the ergonovine test can be useful for evaluating the occurrence of coronary spasm in other unexplained syndromes, such as angina or myocardial infarction with normal coronary arteriograms. Further investigation is necessary to determine whether coronary spasm is produced by increased reactivity of the coronary vessels, a circulating factor, a dysfunction of the autonomic nervous system or some combination of these.[4,40]

Acknowledgment

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Clinical Assessment of Serum Myosin Light Chains in the Diagnosis of Acute Myocardial Infarction

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Serum myosin light chain levels were quantitated with radioimmunoassay in patients admitted to the coronary care unit. In this study there were 29 patients with acute myocardial infarction, 84 with chest pain but without myocardial infarction and 5 with chest pain but with preexisting electrocardiographic abnormalities that could not be interpreted using standard criteria. Values for human cardiac light chains in normal human sera averaged less than 2 ng/ml, and values in the 84 patients without myocardial infarction fell into this category. The 29 patients with myocardial infarction all had elevated light chain concentrations (average 10.9 ± 1.3 ng/ml; range 4 to 35 ng/ml). In this study there were no false positive or false negative results. Use of this assay has permitted separation of patients with and without myocardial infarction. The assay for cardiac light chains provides a biochemical marker of high sensitivity and specificity that is useful in the diagnosis of infarction.

Early and accurate identification of acute myocardial infarction in patients with symptoms and signs suggestive of acute coronary insufficiency remains an important clinical challenge. The diagnosis of myocardial infarction is dependent on the interpretation of historical, electrocardiographic and serum enzyme data. However, each of these variables lacks precision with respect to sensitivity or specificity, or both.[1] Acute myocardial infarction is best recognized when an orderly sequence of repolarization changes in the electrocardiogram is followed by the development of a Q wave or the loss of preexisting R wave potential.[2] New Q wave changes are quite specific for acute infarction but are absent in approximately 30 percent of autopsy-proved cases.[3] The more remote in time the electrocardiogram is taken relative to the acute infarct, the less assurance there is that the diagnosis is definite. The situation is compounded when previous myocardial infarction, which may cancel out some electrical forces, is present.[2] Most physicians now rely heavily on serum enzyme measurement to help define or exclude acute myocardial infarction.[4]

By radioimmunoassay Gere et al.[5] showed that human cardiac myosin light chains are present in increased quantities in the serum of patients with myocardial infarction. In this paper we give the results of our investigation of the clinical application of this assay in diagnosing the presence of myocardial infarction.

Methods

Patients: All 118 patients admitted to the coronary care unit complaining of chest pain are included in this study. All were men ranging in age from 50 to 75 years (average 60). The routine work-up included a complete blood count, urinalysis, electrocardiogram and determinations of serum electrolytes, serum creatine kinase (CK) activity and human cardiac light chain serum levels.

The electrocardiographic criteria for diagnosis of acute myocardial infarction were as follows: (1) Transmural infarction: Q waves more than 0.04 second wide

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TABLE I

Peak Creatine Kinase (CK) and Myosin Light Chain Concentrations (hLC-I) in Patients Admitted to the Coronary Care Unit

Patient Group	Patients (no.)	Observations (no.)	CK ± SEM (IU/ml)	hLC-1 ± SEM (mg/ml)
Control subjects	12	12	121 ± 15	less than 2 ng/ml
Nonmyocardial Infarction	84	227	286 ± 106*	less than 2 ng/ml
Myocardial infarction	29	86	1018 ± 143†	10.9 ± 1.39†
Other	5	15	408 ± 133‡	5.2 ± 0.35†

* No significant difference from values in control subjects ($P < 0.5$).
† $P < 0.001$ compared with values in nonmyocardial infarction group.
‡ No significant difference from value in nonmyocardial infarction group.

and 25 percent of the R waves in depth, S-T segment elevation and T wave inversion. (2) Subendocardial infarction: S-T segment depression with T wave inversion without Q waves but with serum enzyme elevations. The diagnosis of myocardial infarction was based on electrocardiographic evidence or serum enzyme changes, or both.

Creatine kinase: The serum for CK analysis was obtained on admission and each morning for a 3 day period and values were measured using the A-Gent automated CK test (Abbott Labs, Diagnostic Division, Pasadena, California). All CK values are corrected to 37° C. Normal values by this protocol are 36 to 188 international units (IU)/liter.

Cardiac myosin light chains: Cardiac light chains were prepared using normal human cardiac and skeletal muscle myosin obtained within 12 hours of death. These were isolated with the procedure of Wikman-Coffelt et al.[6] and further purified with ion exchange chromatography using Sephadex A-50.[7] Light chains from both muscles were isolated with the method of Weeds and Lowey[8] and purified with ammonium sulfate precipitation[9] and ion exchange chromatography.[10] The purity of the light chain components was assessed with sodium dodecyl sulfate (SDS) gel electrophoresis according to the method of Weber and Osborn[11] using 10 percent acrylamide gels.

Antisera against cardiac light chains were prepared with the aid of Freund's Complete Adjuvant (Calbiochem) and injected into New Zealand White rabbits at various schedules and doses. After a given time, 20 to 30 ml of blood was collected from the marginal vein of the ear and the serum was separated from the cell material and stored frozen without preservatives.

Purified human cardiac light chains were iodinated using the conventional chloramine-T method of Hunter and Greenwood[12] to a theoretical specific acitivity of 100 to 150 μCi/μg. The reaction products were separated on a precalibrated 0.9 by 90 cm column of Sephadex G-100, and appropriate fractions were pooled and frozen. The immunoassay was performed in duplicate in a phosphate-buffered saline solution containing 0.1 percent bovine serum albumin and a 1:100 dilution (final) of nonimmune rabbit serum. A total of 30 to 40,000 cpm (1.1 ng/ml) of iodine-125–labeled light chain I, and a 1:16,000 dilution (final) of light chain antiserum was added to each tube. For the purpose of constructing a standard curve, various concentrations of unlabeled cardiac and skeletal light chains, as well as cardiac myosin, were prepared for each assay. The mixture was incubated at 37° C for 1 hour and then was cooled to 4° C. Antibody-bound material was separated from free material by the double antibody method using sheep antirabbit gamma globulin. The resulting immunoprecipitate was separated by centrifugation and counted in a well-type gamma counter until the counting error was less than 2 percent (Packard Instrument, Inc.). The standard curve was plotted as a normalized percent of initial (B/B_0) counts versus concentration of protein. The complete details of this assay will be presented elsewhere.[5] The assay for patients was performed in duplicate using a total volume of 0.2 ml of an aliquot of each serum drawn for CK analysis.

Control subjects: Twelve normal adults, seven men and five women who ranged in age from 20 to 27 years and had no history of heart disease, were utilized as control subjects.

Results

Chest pain without myocardial infarction: Of the 118 patients, 84 did not meet the electrocardiographic criteria for myocardial infarction (nonmyocardial infarction group). From 227 measurements the CK value was found to be 286 ± 106 IU/liter (range 20 to 8,640) (Table I). From the same number of measurements, each performed in duplicate, no detectable light chains were present, except for the following patient.

Elevated serum light chains in absence of clinical signs of myocardial infarction: This patient included in the 84 patients without a myocardial infarction was found to have had an acute myocardial infarction at autopsy. There was no electrocardiographic evidence of infarction (hence, his inclusion in this group) and no elevation of serum CK levels. However, the light chains were elevated (15 ng/ml). At postmortem examination the heart weighed 710 g; it was massive, globular and of soft, flabby consistency with a granular epicardial surface and focal petechial areas along the anterior margin of the right ventricle. The endocardial surfaces were smooth and glistening with the exception of mural thrombi along the anteroseptal portion of the left ventricle and the adjacent right ventricle. The cut surface of the myocardium showed zones of pallor and yellow-green discoloration of the endocardial aspect of the left and right ventricles; the greatest extent of infarct from base to apex approximated 9 cm. The coronary arteries exhibited severe narrowing and focal calcification with approximately 90 percent luminal narrowing of the left anterior descending coronary artery and approximately 80 percent narrowing of the right coronary artery. The left circumflex artery was narrowed by only 60 percent.

Microscopic examination showed a mural thrombus with early organization. The underlying muscle showed necrosis with inflammatory infiltrate. The anatomic age of the infarct was estimated to be 3 to 4 days.

Acute myocardial infarction: Of the remaining 34 patients, 29 met the electrocardiographic criteria for acute myocardial infarction; 3 of these were diagnosed as having a subendocardial infarct and 26 a transmural infarct. All 29 patients had elevated serum light chain

values, whereas only 24 had abnormal CK levels (Table I). From 86 measurements the peak average CK value was 1,018 ± 143 IU/liter; from the same number of measurements, each performed in duplicate, the peak average light chain concentration was 10.9 ± 1.3 ng/ml (range 4 to 35) (Fig. 1). These values were significantly elevated above normal levels ($P < 0.001$).

Uncategorized cases: The remaining five patients included in this study were not categorized because of preexisting abnormalities that prevented making a definitive electrocardiographic diagnosis. All of these patients had elevated light chain concentrations (5.2 ± 0.35 ng/ml average), whereas only three had elevated CK values (598 ± 91.4 IU/liter average).

Control subjects: The radioimmunoassay of light chains from the normal control subjects yielded undetectable amounts and the CK values of these subjects were within normal limits. There was no statistical difference between male and female subjects.

Discussion

The patient presenting with chest pain and electrocardiographic evidence of Q waves or loss of R waves offers no problem in the diagnosis of myocardial infarction. When the electrocardiogram is not diagnostic, other available data such as serum CK and LDH enzyme and CK-MB isoenzymes and myoglobin determinations may aid in the diagnosis of acute myocardial infarction. However, serum CK levels can be elevated by strenuous exercise, chronic alcoholism, convulsions, pulmonary disease, electrical cardioversion, cerebral vascular disease and intramuscular injections.[13–19] CK-MB isoenzyme values, although high in specificity and sensitivity, are limited to patients seen early with infarction, and Blumberg et al.[20] have reported 6 percent false negative CK-MB isoenzyme value in patients with acute myocardial infarction. Skeletal muscle myoglobin has been shown to be immunologically and chemically identical to cardiac myoglobin.[21] Elevated myoglobin levels have also been noted after cardiac resuscitation, grand mal seizure, trauma and diminished peripheral perfusion of diverse origins.[22] Thus, although many biochemical techniques are available, all have some serious shortcomings.

Of the 118 patients in our study, 84 were judged not to have myocardial infarction by electrocardiographic criteria. A variety of cardiac and noncardiac diagnoses were made in these patients, including arteriosclerotic heart disease, various arrhythmias, cardioversion for tachyarrhythmia, gallbladder disease, pulmonary embolism and alcohol-related liver disease. All but one patient had cardiac light chain concentrations not significantly different from those of the control group. The average serum CK value of these patients was also not significantly different from control values. However, 20 of these patients had elevated CK levels, giving a false positive incidence rate of 24 percent, which is consistent with the findings of Wagner et al.[1] and Galen.[23] Electrocardiographic changes diagnostic of myocardial infarction were present in 29 of the remaining 34 patients, and all 29 had light chain concentrations significantly higher than those of the noninfarction and control groups. Five of these had normal CK levels, giving a false negative incidence rate of 18 percent.

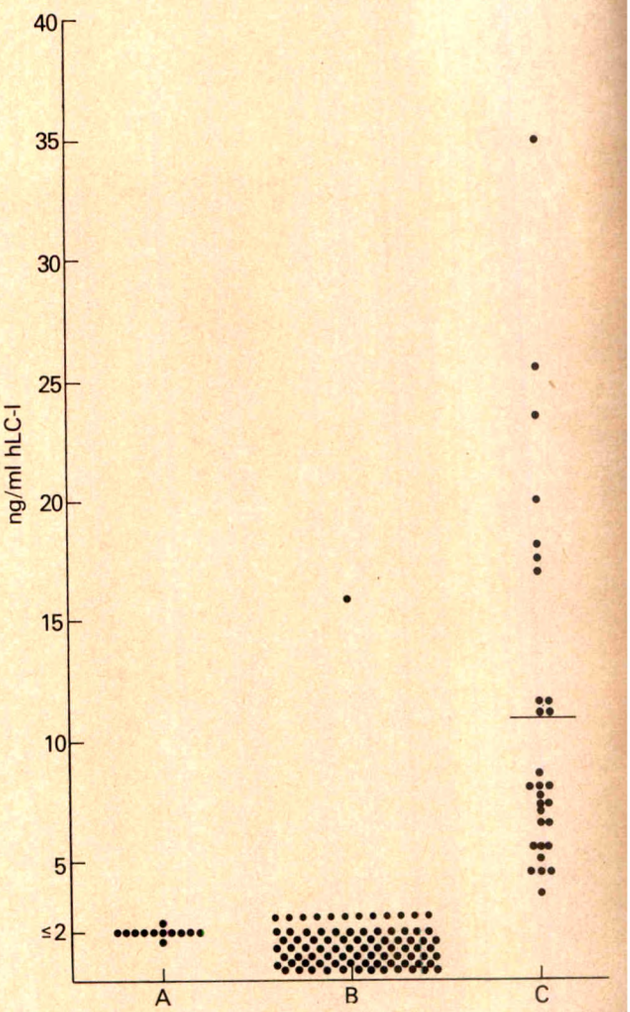


FIGURE 1. Peak average serum light chain concentration (hLC-I) in subjects studied. **A,** 12 control patients; **B,** 80 patients without an electrocardiographic diagnosis of myocardial infarction; **C,** 29 patients with an electrocardiographic diagnosis of infarction. The **horizontal line** in **C** represents the peak average serum light chain concentration in patients with acute myocardial infarction.

The five remaining patients could not be placed in either the myocardial infarction or the nonmyocardial infarction group because of preexisting electrocardiographic abnormalities. All of these had elevated light chain concentrations, but only three had elevated CK levels. If the presence of elevated light chain levels does, in fact, reflect myocardial damage as our data presented indicate, then these patients could reasonably be placed in the myocardial infarction group.

Cardiac myosin light chain assay as a marker of myocardial infarction: As stated by Ahumada et al.,[24] a biochemical marker of myocardial infarction should be specific for cardiac muscle, consistently and rapidly released in the serum, easily measured and have definable kinetics of release into and disappearance from the serum. We believe that the assay for cardiac myosin

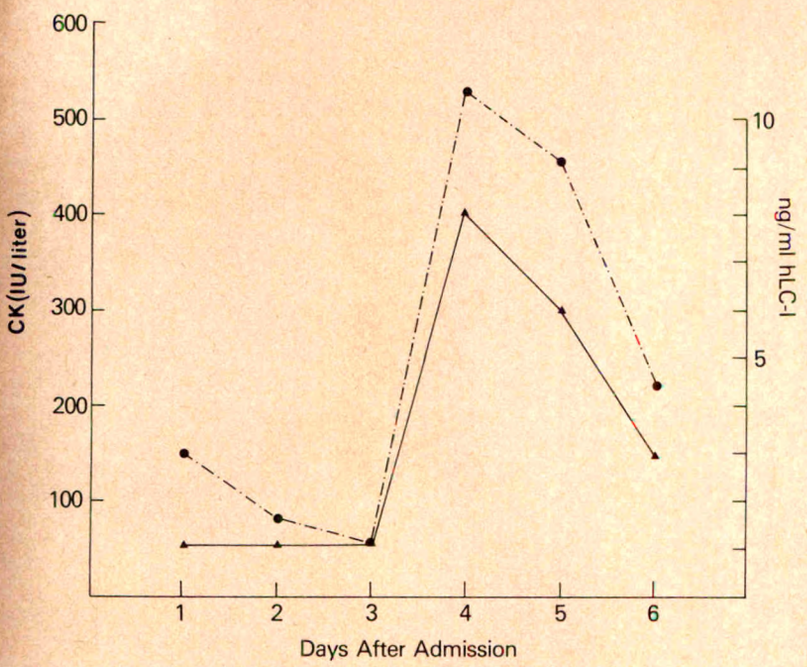


FIGURE 2. Time course study of a patient with an acute anterior wall infarction. Blood was withdrawn every morning on the days indicated after the initial admission on day 0. **Closed circles** = total serum creatine kinase (CK) activity; **closed triangle** = total serum cardiac light chain concentration (hLC-I).

light chains meets these criteria as a marker for the following reasons:

(1) It has been established[25] that cardiac myosin light chains are biochemically distinct from skeletal myosin light chains on the basis of peptide fingerprinting, amino acid analysis and SDS gel electrophoresis. Furthermore, immunologic specificity of light chains has been demonstrated.[26] In this connection using our radioimmunoassay for cardiac light chains we had the opportunity to study the serum of a patient with multiple traumatic injuries with a serum CK level of 44,000 IU/liter. The light chains in this patient's serum were clearly of skeletal muscle origin.[5]

(2) That increased quantities of light chains are consistently released into the serum of patients with myocardial infarction is evident from our finding that all of our patients with myocardial infarction had elevated serum levels of cardiac myosin light chains. On the other hand, all but one patient in the group without infarction had serum light chain levels similar to those of the healthy control subjects. This one exception was a patient with myocardial infarction proved at autopsy who was placed in the noninfarction group because of the absence of electrocardiographic and enzyme changes. This patient had significantly elevated serum light chain levels but did not have increased serum CK.

(3) A limited number of serial determinations in patients with acute myocardial infarction show that the cardiac myosin light chains appear rapidly in the serum. Figure 2 shows a typical time course study of one patient with an acute anterior wall infarct. The appearance of cardiac light chains is closely parallel to that of total CK. In fact, there is a strong correlation between total CK activity and light chain concentration (Fig. 3) in patients with acute myocardial infarction. In preliminary studies with dogs, we find that iodine-125–labeled light chains also disappear from the serum at a rate similar to that seen for CK (Likos J, Colt J and Gere JB, unpublished observations). Additional studies are currently underway to define more clearly the kinetics of the appearance and disappearance of the human cardiac myosin light chains from the serum in patients with myocardial infarction. These studies may also lead to better means of quantitating infarct size.

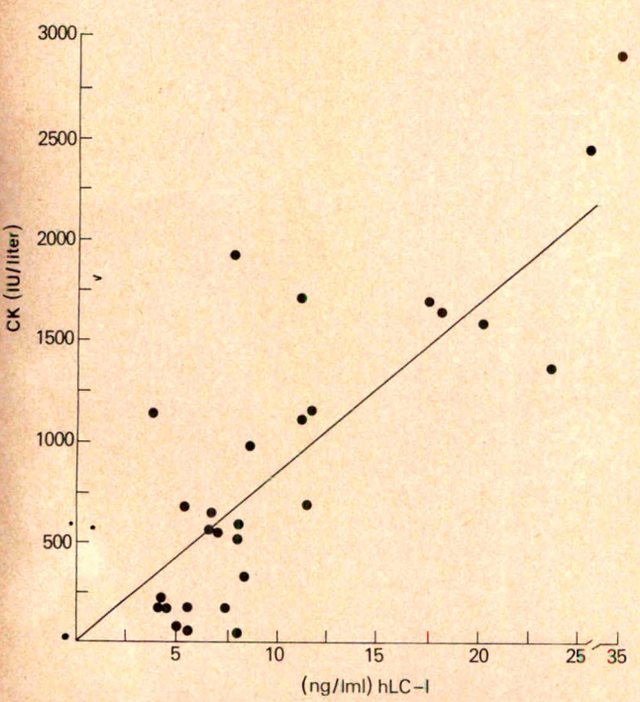


FIGURE 3. Correlation of peak average serum creatine kinase (CK) and myosin light chain concentration (hLC-I) in patients with an electrocardiographic diagnosis of myocardial infarction. The equation for the correlation is: $y = 84.0 x + 8.33$; $r = 0.831$; $P < 0.001$.

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Shape of the Human Cardiac Ventricles

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Previous studies suggest that intramural myocardial architecture is arranged to maximize the efficiency of contraction. To examine the topography of the cardiac ventricles for a possible similar functional economy, measurements were made of the heart weight and ventricular wall curvature, thickness, chamber volumes and axial diameters in 80 hearts, with and without ventricular dilatation or hypertrophy, or both, that had normal coronary arteries and no myocardial lesions. Hearts in various positions of contraction were studied after postmortem arteriography and fixation in distension. Indexes of curvature-thickness were calculated from the measurements using the Laplace relation. The ventricles consist of three mutually intersecting curved partitions, right and left free walls and interventricular septum, which are segments of prolate spheroids. The septum usually curves so as to function as part of the left ventricle but is thinner and flatter than the free wall. Indexes of curvature-thickness showed that in the distended position ventricles are more globular and thin-walled; in the contracted position they are more cylindrical and thicker. The left ventricular free wall index showed greater change between distension and contraction than the other components.

The results suggest that ventricular configuration is a compromise between a spherical shape that would need the least energy for diastolic ventricular filling and a tubular shape that would permit maximal conversion of systolic myocardial muscle cell tension into cavitary pressure increase. Ventricular topography probably develops as that geometry that requires the minimal energy expenditure in the overall economy of the circulation. Clinical determination of curvature-thickness indexes, similar to the postmortem indexes studied here, may find practical implementation in the assessment of cardiac diseases with two dimensional echocardiography and radionuclide imaging.

The growth of heart muscle is a direct function of its work load,[1–3] and the arrangement of muscle cells within the myocardium appears to reflect an adaptation for achieving the optimal effectiveness of conversion of the energy of ventricular contraction into an increase of pressure in the blood contained in the ventricular cavity.[4] If such an adjustment for obtaining mechanical efficiency for a given work load is true of the architectural arrangement of the myocardium, then it is not unreasonable to seek a similar adaptation of the overall configuration of the cardiac chambers to the extraction of the greatest possible proportion of the force of ventricular contraction for the propulsion of the ejected blood. The basic formula for understanding the shape of the heart relative to its work load is the law of Laplace, which states that for thin-walled spheres wall tension is proportional to pressure and radius of curvature. However, because the heart is not a thin-walled sphere with a uniform radius, one can make only an approximate application of the Laplace equation to the heart. When the ventricular wall thickness is taken into account it

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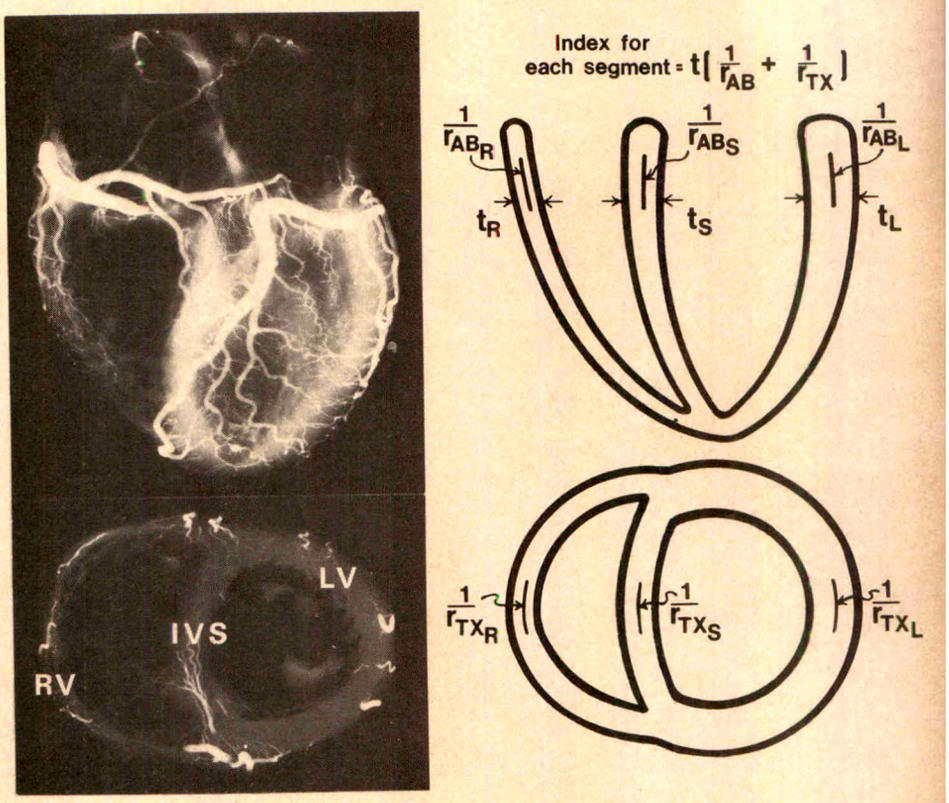


FIGURE 1. Left, postmortem angiograms of a normal intact heart **(top)** and a transverse section of its ventricles **(bottom)** taken at the level of maximal ventricular diameter at which the curvatures and thicknesses were determined for the right ventricle (RV), left ventricle (LV) and interventricular septum (IVS). In the transverse plane the curvatures of the ventricular segments are approximately circular; in the apex to base plane they are approximately elliptical. **Right,** diagram showing how the curvature-thickness indexes for the right (R) and left (L) ventricular free walls and interventricular septum (S) are determined. Wall thickness (t) and curvatures (1/r) in the apex to base (AB) and transverse (TX) planes are determined for each segment at the level of the widest diameter of the left ventricle.

has been shown by detailed study of a few hearts[5,6] that the thickness of the ventricular walls at various points maintains a constant relation to the ventricular radius, and that the ratio of thickness to ventricular radius is linearly related to systolic pressure.

The final shape of the human heart must further reflect an adaptation to the needs of both systole and diastole, states in which both the thickness and curvature of the ventricle drastically change. Almost all forms of heart disease alter ventricular topography and those changes in ventricular configuration may in themselves produce cardiac dysfunction.

In this study we examined the functional economy of the shape of the heart by quantitatively defining the configuration of the cardiac ventricles in a large autopsy series of human hearts that manifested various degrees of distension and contraction. Normal hearts were contrasted to hearts that endured abnormal pressure and volume loads during life to determine the alterations in ventricular configuration that accompany given disease states.

Material and Methods

Selection of cases: The hearts from 850 patients in the autopsy files of The Johns Hopkins Hospital, studied with a standard method employing coronary arteriography and fixation in distention,[7] were reviewed. Cases were included in this study only if (1) two sets of biplane stereoscopic radiographs, one set of the intact heart and one of the transverse "breadloaf" sections of the heart, were available; (2) coronary arterial injections and fixation of the cavities in distension were technically adequate; (3) no vascular abnormality was seen in the angiograms and at most only trivial atherosclerosis had been recorded from gross examination of the multiple transections of the epicardial coronary arteries made at 2 to 3 mm intervals; and (4) no significant focal or diffuse myocardial disease other than hypertrophy had been detected with gross or light microscopic study. Cases with coronary artery disease and myocardial lesions were excluded to avoid errors introduced by regional myocardial injury affecting ventricular shape.

Autopsy procedure: Hearts obtained at autopsy had their coronary arteries injected at a pressure of 100 to 150 mm Hg with a barium-pigment-gelatin mass to which formalin had been added. Upon completion of the injection cannulas were tied into the atria and great vessels, the remaining orifices ligated, and the chambers distended with 10 percent formalin through the cannula at 30 to 40 mm water pressure while the heart was suspended in a container of formalin. After overnight fixation stereoscopic radiographs were prepared of the fixed distended heart and of the transverse sections into which it was sliced. Photographs were prepared. The coronary arteries were transected at 2 to 3 mm intervals and compared with the radiographs. Representative portions of myocardium, including both ventricles and interventricular septum, and of the coronary arteries were taken for histologic examination.

Classification of disease states: On the basis of a review of the clinical records and the gross heart specimens, we determined the patient's age, heart weight and the character of any cardiac disease and assigned each heart to one of four disease groups, as follows: Group 1 (normal), hearts with no evidence of heart disease; Group 2 (left ventricular hypertrophy), hearts with predominant left ventricular hypertrophy, as determined morphologically, that was secondary to resistance to outflow, such as that occurring in systemic hy-

pertension or aortic stenosis; Group 3 (right ventricular hypertrophy), hearts with predominant right ventricular hypertrophy, as determined morphologically, such as that occurring in mitral stenosis or pulmonary disease; and Group 4 (chronic dilatation), hearts with dilatation and hypertrophy of the left ventricle, either idiopathic or secondary to valve disease. Hearts with features of more than one of these disease states were categorized according to the dominant or primary abnormality.

Measurements of ventricular configuration and thickness: From the biplane radiographs the curvature of the ventricular walls and interventricular septum was measured in two perpendicular planes using a plastic transparent plexiglass sheet with inscribed segments of circles of varying curvature that was placed over the radiograph on a viewbox. The best fit was determined by agreement between two observers. The radiographs of the intact heart were oriented so that the interventricular septum was perpendicular to the film and those portions of the free wall of right and left ventricle most distant from the septum appear at the edges of the radiographic image (Fig. 1). The radiographic images of the transverse slices of the heart were oriented at a right angle to those of the intact specimen. Curvature in both the apex to base and transverse directions was determined at the apex to base level of the maximal diameter of the left ventricle. This level was chosen for study because the transverse curvature of the section could be expected to lie in the plane of the radiograph. Sections of ventricular wall taken at other levels with our method of study yield a diagonal section of the wall and would thus give an erroneous measurement. Curvature was determined at the mid thickness of the ventricular walls.

The thickness of the ventricular walls and septum was measured from the radiographs for the points at which curvature had been determined in the two perpendicular directions. The diameter of the left ventricle, including the myocardial wall, was measured at its maximal diameter. The length of the left ventricle was measured between the apex and

TABLE 1

Topographic Data in 80 Human Hearts

	Normal	Left Ventricular Hypertrophy	Chronic Dilatation	Right Ventricular Hypertrophy	Total
Hearts (no.)	17	13	35	15	80
Patient age (yr)	52 ± 16 (20–87)	55 ± 17 (19–77)	46 ± 18 (15–88)	52 ± 14 (25–83)	50 ± 17 (15–88)
Heart weight (g)	319 ± 99 (227–430)	656 ± 124 (430–835)	739 ± 195 (380–1200)	446 ± 90 (265–660)	585 ± 223 (250–1200)
Right ventricle					
Thickness (mm)	7.0 ± 1.0 (5–9)	9.2 ± 1.4 (8–12)	8.4 ± 1.5 (6–12)	9.4 ± 2.8 (5–14.5)	8.6 ± 1.9 (5–14.5)
Curvature					
Apex to base	0.11 ± 0.03 (0.06–0.17)	0.11 ± 0.07 (0.03–0.20)	0.08 ± 0.03 (0.01–0.17)	0.14 ± .05 (0.03–0.25)	0.10 ± .04 (0.03–0.25)
Transverse	0.18 ± 0.06 (0.08–0.33)	0.19 ± 0.06 (0.10–0.33)	0.14 ± 0.03 (0.06–0.20)	0.16 ± 0.06 (0.08–0.33)	0.16 ± 0.06 (0.06–0.33)
Index	0.20 ± 0.05 (0.13–0.31)	0.27 ± 0.07 (0.17–0.36)	0.19 ± 0.04 (0.08–0.27)	0.29 ± 0.11 (0.19–0.60)	0.22 ± 0.08 (0.08–0.60)
Volume (ml)	92 ± 55 (36–200)	80 ± 40 (15–150)	138 ± 60 (60–305)	112 ± 40 (40–180)	120 ± 77 (15–305)
Interventricular septum					
Thickness (mm)	14.6 ± 2.3 (11–19)	22.0 ± 3.9 (16–30)	17.0 ± 3.1 (10–25)	14.6 ± 5.5 (9.5–23)	17.0 ± 4.0 (9.5–30)
Curvature					
Apex to base	0.04 ± 0.05 (0.00–0.14)	0.02 ± 0.03 (0.00–0.08)	0.05 ± 0.04 (0.00–0.17)	0.03 ± 0.05 (−0.05–0.11)	0.04 ± 0.04 (−0.05–0.17)
Transverse	0.27 ± 0.06 (0.20–0.40)	0.20 ± 0.05 (0.07–0.29)	0.20 ± 0.07 (0.07–0.50)	0.16 ± 0.14 (−0.17–0.33)	0.21 ± 0.09 (−0.17–0.50)
Index	0.43 ± 0.13 (0.23–0.77)	0.51 ± 0.18 (0.15–0.78)	0.41 ± 0.15 (0.17–0.86)	0.39 ± 0.38 (−0.16–1.50)	0.43 ± 0.22 (−0.16–1.50)
Left ventricle					
Thickness (mm)	15.4 ± 2.3 (11–20)	22.5 ± 3.9 (15–27)	17.7 ± 2.8 (11–24)	17.2 ± 3.9 (11–23)	17.6 ± 4.4 (11–27)
Curvature					
Axis to base	0.13 ± 0.03 (0.07–0.20)	0.13 ± 0.02 (0.10–0.17)	0.14 ± 0.04 (0.08–0.25)	0.13 ± 0.02 (0.08–0.17)	0.13 ± 0.03 (0.07–0.25)
Transverse	0.37 ± 0.08 (0.25–0.50)	0.31 ± 0.04 (0.25–0.40)	0.27 ± 0.06 (0.20–0.50)	0.36 ± 0.10 (0.20–0.50)	0.31 ± 0.09 (0.20–0.50)
Index	0.81 ± 0.22 (0.51–1.23)	0.98 ± 0.17 (0.74–1.24)	0.73 ± 0.16 (0.46–1.13)	0.86 ± 0.30 (0.47–1.61)	0.81 ± 0.22 (0.46–1.61)
Volume (ml)	74 ± 38 (20–145)	55 ± 20 (25–95)	157 ± 74 (65–335)	69 ± 59 (20–222)	120 ± 110 (20–335)
Length (cm)	9.2 ± 0.9 (8–10.5)	10.1 ± 3.2 (9.5–13)	11.3 ± 1.6 (8–17.5)	9.2 ± 0.9 (8–11)	10.4 ± 1.6 (8–17.5)
Diameter (cm)	6.9 ± 0.8 (5.25–8.5)	8.2 ± 0.6 (6.7–9.0)	9.1 ± 1.1 (6.6–11)	6.7 ± 1.3 (4.5–10)	8.0 ± 1.5 (4.5–11)

* Mean ± standard deviation (range).

the base of the chamber. Ventricular volumes were determined from measurements of water contained in the fixed distended chambers.

Analysis of measurements: The curvature and thickness measurements were analyzed by applying a modification of the Laplace relation. For example, in a soap bubble, the pressure of the contained air is directly proportional to the surface tension of the soap film and to the curvature.[8] Small soap bubbles thus have greater pressure of their contained air than larger bubbles made from the same solution. When two such bubbles are in contact the septum between them develops a curvature that is a function of the difference between the conditions existing in the two bubbles. The relation of the curvature (1/r) of the free walls and septum (S) of two spherical bubbles on the right (R) and left (L), made of the same fluid, is given by the equation[8]:

$$\frac{1}{r_L} = \frac{1}{r_R} + \frac{1}{r_S}$$

If the system of "bubbles" could be constructed so that the walls had different surface tension properties and the two chambers were not spherical, then one would have to introduce factors that took these differences into account. In the case of the cardiac walls one is concerned not with surface tension but with the tensile stress in the wall at the point where the radii of curvature were determined. As a simplifying assumption, we have considered the tension-resisting (diastole) or tension-producing (systole) capacity of the heart wall to be a direct function of wall thickness (t). Curvature of the nonspherical ventricles has been expressed as the sum of the transverse and apex to base curvatures measured at right angles to each other.[9] The equation expressing the relation between curvatures in the apex to base (AB) and transverse (Tx) planes and thickness of the right and left ventricular walls and the septum would be:

$$t_L\left(\frac{1}{r_{L_{AB}}} + \frac{1}{r_{L_{Tx}}}\right) = t_R\left(\frac{1}{r_{R_{AB}}} + \frac{1}{r_{R_{Tx}}}\right) + t_S\left(\frac{1}{r_{S_{AB}}} + \frac{1}{r_{S_{Tx}}}\right)$$

An index was calculated for each portion of the heart wall, corresponding to the three terms in the preceding equation, from the thickness and curvature measurements made from the radiographs.

Results

The mean, standard deviation and range of values for the major features of the 80 cases meeting the criteria for inclusion in this study are given in Table I. Hearts with the largest average weight, ventricular volumes and left ventricular dimensions were in Group 4 (chronic dilatation). The greatest average left ventricular and interventricular septal thickness was seen in Group 2 (left ventricular hypertrophy), but the greatest average right ventricular thickness was found in Group 3 (right ventricular hypertrophy). In all hearts the length of the left ventricle exceeded its diameter.

Indexes of ventricular curvature: Curvature values (the reciprocal of radius of curvature) for the free walls of both ventricles fell within rather narrow limits. In making the measurements it became apparent that the ventricles generally consist of three intersecting curved planes. In the transverse plane the segments are approximately circular and in the apex to base plane they approximate an ellipse (Fig. 1). For the apex to base plane the point of maximal transverse diameter, where measurements were made, corresponds to the minor axis of the ellipse. It is appropriate to regard each of the three portions constituting the ventricular walls as portions of prolate spheroids, that is, the figures generated by rotating an ellipse about its long axis.

The right ventricular free wall showed more morphologic variations than the other segments. It frequently had two portions, a flatter less curved diaphragmatic aspect and an anterior-marginal wall component. The measurements made here were in the more curved anterior-marginal part that also contained the apex to base curvature that was measured. The interventricular septum had the same constancy of curvature within a given plane seen in the free walls but had a greater range of curvature. Several septae were straight (zero curvature) in the apex to base direction and one was concave to the right (negative curvature). Similarly, the curvature in the transverse plane ranged from negative to very concave toward the left ventricle. Usually the maximal curvature was found in the transverse plane of the left ventricular free wall and the least curvature in the apex to base plane of the interventricular septum. The curvature-thickness indexes for the three components of the heart wall showed a wide range of values for all hearts studied (Table I).

Curvature-thickness indexes: The cardiac ventricles at autopsy may be fixed by rigor mortis at any position of distension.[7] The postmortem ventricles may be in any state ranging from complete distension to complete contraction, which may represent the state of the cardiac chamber when rigor mortis occurred (Fig. 2). Also, the two ventricles may have different degrees of distension: one may be distended and one contracted, independent of each other. Because the ventricular wall thickness and curvature change as the wall moves from the distended to the contracted position the curvature-thickness index varies for the same part of the heart wall with different degrees of distension. To compensate for this factor the ventricles in each heart were graded for their position of distension on a scale of 0 to 4+. Zero was the position of complete or almost complete cavity obliteration corresponding to extreme contraction. The maximal position of extreme distension corresponds to 4+. Other ventricles were considered to be in a midposition either on the contracted (2+) or the distended side (3+). The assessment was made on the

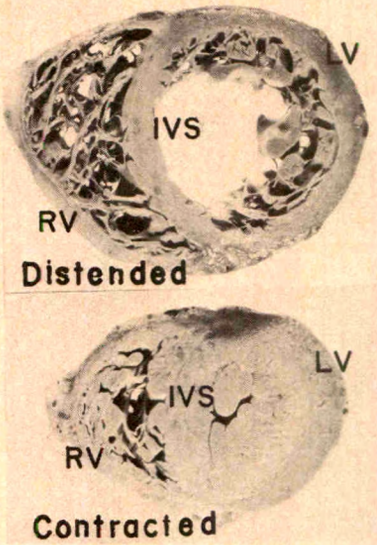


FIGURE 2. Transverse sections taken at the same level of the ventricle of two normal hearts of similar weight. The ventricles of one **(top)** are both in the extreme distended position, those of the other **(bottom)** are in extreme contraction. IVS = interventricular septum; LV = left ventricle; RV = right ventricle.

basis of trabecular and papillary muscle position relative to the compact portion of the ventricular wall.

Depending on the position of distension, the measured wall thicknesses, curvatures, curvature-thickness indexes, chamber volumes and left ventricular lengths vary as shown in Table II. With distension, wall thickness is least, cavity volume greatest and the index lowest. When the ventricle is contracted, the apex to base curvature of both free walls is least and the transverse curvature greatest.

The curvature-thickness indexes of the three components of the ventricular walls were compared for those 11 hearts with both ventricles in the markedly contracted position and the 26 hearts with both ventricles in the markedly distended position (Table III). With this further constraint the sum of right ventricular and interventricular septal indexes nearly equals the left ventricular index when the ventricles are distended. However, during contraction the major change in the curvature-thickness index is seen in the left ventricular free wall, which becomes thickened and more curved.

Discussion

Ventricular Topography

The study shows that the human cardiac ventricles can be thought of as three intersecting doubly curved partitions (Fig. 3). Each partition appears to approximate a segment of a prolate spheroid, being circular in the transverse plane. The left ventricular free wall is thickest and has the greatest curvatures in both the transverse and apex to base directions (Table I). The right ventricular free wall is thinnest but has curvatures only slightly less than those of the left ventricular free wall. The interventricular septum is usually slightly less thick than the left ventricular wall but has smaller curvatures. The septum is curved so that it usually functions as a component of the left ventricle. In some hearts its net curvature approaches zero; that is, the septum is straight, and in this situation the thickness tends to be less than usual. In one heart studied the net curvature of the septum was reversed so that this component of the heart wall functioned as part of the right ventricle.

In the distended position the three components of the ventricular walls have curvature-thickness indexes that approximate the behavior that would be expected in soap bubbles. The ventricular partitions are curved relative to each other as though their configuration were determined by the mural tension engendered by the

TABLE II

Variation in Ventricular Topography With Stages in Cardiac Distension*

	Contraction (0 or 1+)	Mid Position		Distension (4+)
		2+	3+	
Right ventricle				
Hearts (no.)	14	14	19	33
Thickness (mm)	10.0 ± 1.9	9.4 ± 2.4	8.7 ± 1.5	7.7 ± 2.4
Curvature				
Apex to base	0.08 ± 0.05	0.09 ± 0.05	0.11 ± 0.06	0.11 ± 0.03
Transverse	0.17 ± 0.06	0.16 ± 0.03	0.16 ± 0.06	0.16 ± 0.06
Index	0.28 ± 0.15	0.23 ± 0.07	0.23 ± 0.07	0.20 ± 0.05
Volume (ml)	68 ± 22	106 ± 40	109 ± 51	136 ± 64
Interventricular septum				
Hearts (no.)	21	13	13	33
Thickness (mm)	20.7 ± 3.6	16.2 ± 4.0	16.8 ± 3.0	15.1 ± 3.0
Curvature				
Apex to base	0.03 ± 0.03	0.02 ± 0.03	0.04 ± 0.04	0.06 ± 0.05
Transverse	0.20 ± 0.09	0.18 ± 0.12	0.22 ± 0.08	0.21 ± 0.08
Index	0.49 ± 0.21	0.40 ± 0.38	0.42 ± 0.12	0.40 ± 0.16
Left ventricle				
Hearts (no.)	21	13	13	33
Thickness (mm)	21.6 ± 3.0	17.7 ± 4.0	17.6 ± 2.9	15.9 ± 2.7
Curvature				
Apex to base	0.13 ± 0.02	0.13 ± 0.03	0.13 ± 0.02	0.14 ± 0.04
Transverse	0.35 ± 0.08	0.33 ± 0.09	0.31 ± 0.11	0.28 ± 0.06
Index	1.04 ± 0.21	0.81 ± 0.11	0.80 ± 0.11	0.67 ± 0.15
Volume (ml)	62 ± 39	76 ± 40	104 ± 86	153 ± 73
Length (cm)	9.9 ± 1.4	10.1 ± 1.5	10.6 ± 2.4	10.7 ± 1.2
Diameter (cm)	7.3 ± 1.0	7.8 ± 1.9	7.9 ± 1.6	8.7 ± 1.3

* Mean ± standard deviation.

TABLE III

Ventricular Wall Curvature Thickness Indexes for Hearts With Both Ventricles in Either Extreme Contraction or Extreme Distension*

Position of Ventricles	Hearts (no.)	Age (yr)	Heart Weight (g)	Indexes		
				Right Ventricle	Inverventricular Septum	Left Ventricle
Contraction (0 or 1+)	11	55 ± 18	570 ± 184	0.28 ± 0.13	0.50 ± 0.19	1.11 ± 0.23
Distension (4+)	26	45 ± 20	565 ± 249	0.19 ± 0.05	0.37 ± 0.04	0.66 ± 0.15

* Mean ± standard deviation.

distending pressure of the ventricular contents. During contraction the most change in curvature-thickness index is found in the left ventricular free wall partition, which thickens, straightens in the apex to base direction and increases curvature in the transverse plane (Table II), suggesting that mural tension engendered by contraction of the myocardium in this segment plays the greatest role in elevating intracavitary pressure.

Relation of Postmortem Topography and Ventricular Function

The curvature thickness relations studied here were based on the positions in which the cardiac ventricles are fixed in rigor mortis. All of the factors that determine the position of the ventricular wall are unclear, but in a previous study[7] it was suggested that their position was determined largely by the volume of blood entering the cavity after the last ventricular systole. It is probable that the distended and contracted positions of the postmortem ventricle do not exactly correspond to diastolic and systolic positions of the living ventricle. However, the general relations of the curvature-thickness indexes of the ventricular segments will be similar in the two states.

As the relaxed ventricle of diastole is distended by the blood entering its cavity from the atrium and venous return, any point of the ventricular wall will resist distension (that is, develop tension) as a function of the pressure energy of the entering blood and the local curvature of the ventricular wall at that point. This relation is described by the Laplace equation:

Diastolic Wall Tension
$\propto$ Diastolic Pressure of Intracavitary Blood
$\times$ 1/Curvature

The extent to which the wall is distended at any point will also depend on the wall thickness; and the degree of diastolic filling of the ventricular cavity at any site will be proportional to the pressure of entering blood (that is, preload) and local wall curvature and wall thickness inversely. The thicker and more curved the ventricular wall, the more resistance there will be to filling of the cavity. This relation is only an approximation, because curvatures will vary through the thickness of the heart walls.

When the ventricles contract in systole, there is a transfer of energy from the shortening muscle to the blood contained in the cavity. At any point on the ventricular wall the conversion of tension in the muscle cells to pressure in the cavity also follows the Laplace relation:

Systolic Pressure of Intracavitary Blood
$\propto$ Systolic Wall Tension $\times$ Curvature,

and the intracavitary pressure will be directly proportional to tension in the muscle cells and the curvature in the cells. The greater the curvature, the greater the proportion of energy that is transferred to the intracavitary blood. If the muscle cell was straight, that is, had zero curvature, there would be no energy transfer. The less the curvature for a given point on the ventricular wall, the less transfer of energy occurs from individual cells to the blood. The total energy transferred at a given site on the ventricular wall will depend on the thickness of muscle at that point. Utilizing these concepts, we can approach both the problem of the shape of the normal developing heart and the remodeling process seen in diseased and malformed hearts.

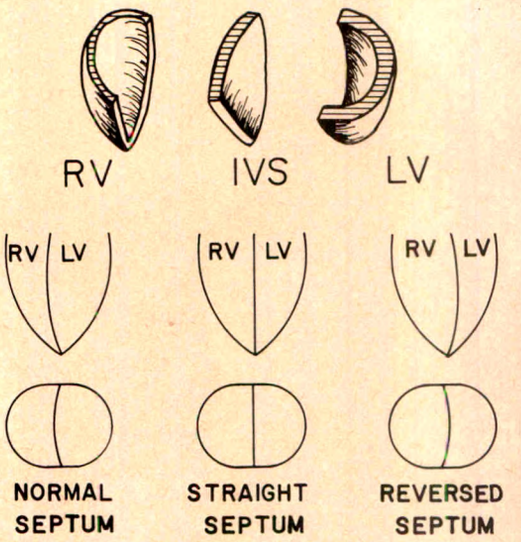


FIGURE 3. Diagram of the three segments of the prolate spheroids that constitute the ventricular walls. The three configurations of the interventricular septum observed are shown at **bottom.** Abbreviations as in Figure 2.

Applications to Developing and Diseased Hearts

Developing hearts: In the developing heart, it is probable that repetitive interaction of the responses of the ventricular walls to diastolic and systolic pressure, tension and curvature-thickness interrelations produce the cardiac configuration. During cardiogenesis, diastolic filling of the ventricles would tend to induce a spherical configuration analogous to two soap bubbles in contact.

In contrast to postnatal growth, which takes place by enlargement of muscle cells or hypertrophy, a size increase in the growing fetal heart occurs by proliferation of muscle cells.[10] The cells that are generating the most tension appear to be the ones that grow and replicate to the greatest extent,[11,12] leading to a selection for muscle cells that are oriented so as to generate the most systolic tension. The ventricular wall consists of concentric layers of muscle cells, each of which has slightly different average angles of orientation of its fibers to its neighbor.[4] The fibers that appear mainly responsible for reducing cavity size and therefore generate the most tension are mid mural and oriented transversely around the ventricle, and these transverse muscle bundles constitute the major portion of the wall thickness, especially of the left ventricle.[4,13] Thus, in the growing ventricle, proliferation of the fibers oriented around the more curved circular transverse section would be favored by the greater pressure produced by these muscle cells in comparison with less curved apex to base oriented fibers, which generate less tension. The final

ventricular configuration must therefore represent an interaction of the diastolic, passive acquisition of soap bubble-like curvatures of the three septa, and the systole-induced active growth of muscle cells to generate a uniform pressure throughout the variously curved segments of the ventricle.

Diseased hearts: The hearts studied here show that further modification of the normal ventricular configuration may be produced by disease (Fig. 4). Hearts with predominant left hypertrophy have an increase in the average curvature-thickness index of all three segments of the wall. The major factor leading to the greater indexes is increased wall thickness. This alteration is accompanied by an overall average doubling of weight and increase in ventricular length and diameter, but no change in ventricular volume. The heart with chronic dilatation shows a decreased index and, compared with the normal heart and the heart with left ventricular hypertrophy has a wall too thin for the ventricular size. It is possible that the declining ability of some chronically dilated hearts to perfuse the systemic circulation adequately, that is, to generate pressure, is related to this disproportion. In right ventricular hypertrophy there is an increased right ventricular index resulting from an increased thickness of that ventricle. The interventricular septa in these hearts showed curvature variations, in some cases with the direction of curvature in one or the other plane being reversed, so that the septum formed a component of the right ventricle. Whether such curvature variations of the septum induce left ventricular dysfunction remains to be determined.

Clinical implications of ventricular topography: Understandably, the variations in ventricular topography appear to reflect the underlying disease state, whether it be aortic stenosis, idiopathic myocardiopathy or pulmonary disease. Therapeutic interventions must be directed in large part at preventing irreversible topographic changes in the heart, and correcting them wherever possible. For example, in many forms of valve disease it may be unwise to wait to replace severely diseased valves until symptoms develop. Following up the progression of curvature-thickness indexes in both transverse and apex to base planes in systole and diastole may allow a more precise evaluation of the sequence of development of altered topography that can be correlated with clinical symptoms and processes in certain disease states. Until now, we have been limited by our diagnostic tools: The physical examination, chest radiograph, and electrocardiogram provide relatively crude measurements of cardiac size. With the recent development of the more sophisticated noninvasive techniques of two-dimensional echocardiography[14] and radionuclide imaging[15,16] of the heart, it is now feasible to make such sequential determinations of curvature-thickness indexes. It is likely that these determinations will be useful not only in following up the progression of disease, but also in defining more precisely the work load imposed primarily by the alterations of heart shape associated with various diseases, including myocardial infarction, primary and secondary myocardiopathy and congenital malformations.

Interpretation of Ventricular Shape Based on the Principle of Minimal Work

Ventricular morphology related to energy expended: Because the development of ventricular configuration appears to be derived from the interplay of tension-pressure-curvature-thickness factors during diastole and systole, it is reasonable to ask if the normal cardiac configuration is an advantageous one. From the point of view of the organism as a whole such "advantage" may be understood as being the performance of function with minimal energy expenditure.[17] It has

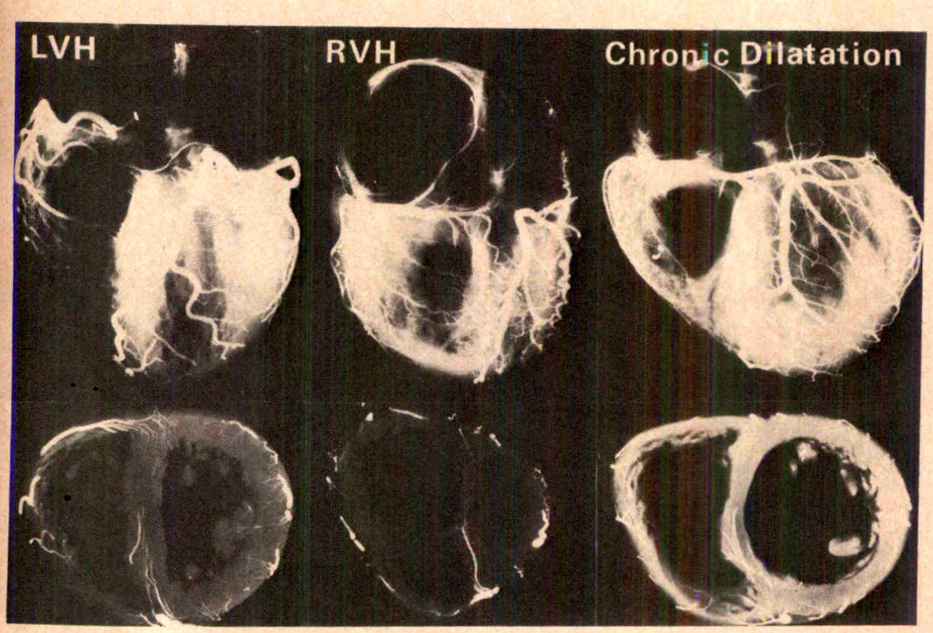


FIGURE 4. Alterations in the ventricular shape introduced by disease states. In left ventricular hypertrophy (LVH) the increased thickness of the left ventricular free wall and septum increases their indexes commensurate with the increased pressure generated by the left ventricle. A similar alteration occurs in the right ventricle with right ventricular hypertrophy (RVH). In the example shown the septum is nearly straight and, because it does not contribute to pressure generation in either the right or the left ventricle, it is also thin. In chronic dilatation there is marked hypertrophy but the ventricular dilatation reduces the curvature-thickness indexes to less than normal. The low indexes correlate with the reduced functional capacity of these ventricles.

previously been shown that the morphologic features of sections of the vascular tree appear to satisfy conditions of minimal energy expenditure to perform their function.[18] The notion that vessel size is adjusted to its most efficient caliber may be extended to ventricular inlet and outlet ports and is supported by the rather narrow range of valve diameters actually observed and the similarity in the sizes of the aorta and pulmonary artery,[7] which carry similar flow levels. Similarly, the caliber of the ventricles should permit efficient blood flow through their inlet and outlet ports without pressure gradients, within the constraints imposed by the intrinsic characteristics of cardiac muscle cell function. It is assumed that ventricular muscle mass remains constant throughout the cardiac cycle and that the visco elastic properties of the muscle are unchanged. The energy expended by the ventricles during a cardiac cycle will be the sum of four factors: (1) the energy required to fill the ventricle during diastole; (2) the energy required to increase intracavitary pressure to the systolic level and to eject the stroke volume; (3) the energy required to create and maintain the muscle mass that accomplishes systolic ejection; and (4) the energy required to create and maintain the blood that fills the ventricle. Diastolic filling energy would be least if the ventricle were a large thin-walled sphere, whereas systolic ejection energy would be least for the ventricle with its muscle cells most curved relative to the contained blood, that is, a long narrow cone. Sustenance of both myocardium and blood would be least for the ventricle that contained the smallest volume.

The third component of energy requirements, the muscle mass, is more or less invariant over a range of possible cardiac shapes. One can view the ventricle as a stack of muscular anuli of variable radius. By assuming that wall thickness, t, is proportional to tension achieved, T, against a constant pressure, P, throughout the ventricle, we can employ the Laplace relation, $t \propto T = Pr$, to argue that wall thickness at each anulus is proportional to the interior radius, r, at that anulus. The myocardial mass in this negligibly tall and negligibly thick anulus is proportional to the wall thickness times radius, whereas the volume of blood is proportional to the radius squared. In other words, a larger radius (which requires a thicker myocardium to achieve the required pressure) delivers a proportionately greater volume of blood, so that the work of muscle maintenance is invariant whether one is dealing with a tall stack of narrow anuli, a short stack of wide anuli or some intermediate structure.

With regard to the blood volume of the ventricle, it is well recognized that within a wide range of cardiac sizes in various species and with a variety of measuring techniques the ventricular ejection fraction is found to be about 60 percent.[19] This value is similar to the 60 percent found in our study comparing average ventricular volumes of hearts in contracted and distended positions (Table II). Although the complete explanation of the ubiquity of the 60 percent ejection fraction is unclear, it probably relates to the properties of cardiac muscle cells that determine the relation of developed tension, velocity of contraction and muscle cell length. For purposes of the present argument, we may assume that there is some "best" interrelation of these three factors that is manifested by the 60 percent ejection fraction.

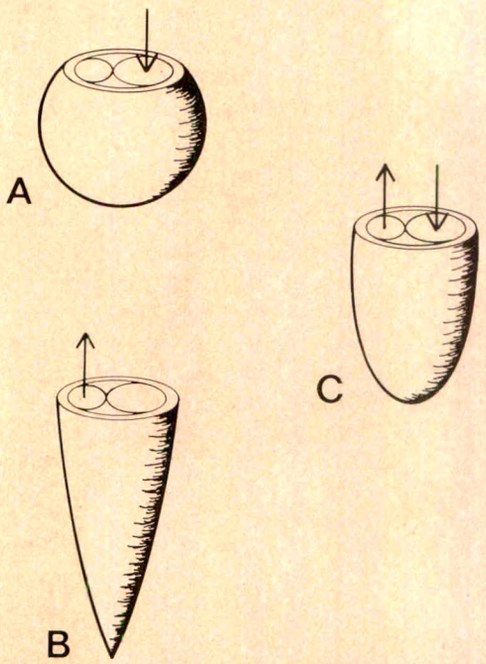


FIGURE 5. Diagram of possible ventricular shapes, all with the same inlet-outlet port. **A,** a spherical ventricle would require the least expenditure of energy for diastolic filling. **B,** a nearly conical ventricle would be more efficient for systole because the curvature of muscle cells is increased allowing a greater transfer of the energy of contraction to increasing intracavitary pressure. **C,** the prolate hemispheroid is the shape that would minimize the sum of energy expenditures in diastole and systole and is also the shape that most closely resembles the normal human left ventricle.

Characteristics of efficient ventricular topography: We would predict that an efficient ventricle, built of standard cardiac muscle cell building blocks, would have certain characteristics: (1) The ventricle should eject about 60 percent of its volume in systole; (2) to reduce energy loss at pressure gradients the cross-sectional dimensions of the ventricle in diastole and systole should be similar to the sizes of inlet and outlet ports, respectively; and (3) because the energy used in the cardiac cycle is the sum of diastolic filling, systolic emptying and a constant for maintenance of the mass of muscle and contained blood, the most efficient topography should be a compromise between a spherical diastole-determined shape and a conical systole-determined configuration. This range of shapes constitutes prolate spheroids (Fig. 5); at one end of the spectrum is the sphere and at the other end an elongated almost conical cigar-shaped structure. The most efficient topography would be located on the spectrum of shapes so as to minimize the combined energy expenditures of systole and diastole, and it would be a prolate hemispheroid.

Inspection and measurement of hearts at autopsy

shows that ventricular topography corresponds to these predicted specifications. The three components of the ventricular walls appear to be segments of prolate spheroids. For the left ventricle the inlet and outlet ports are adjacent to each other and fill the opening of the ventricular cavity. The maximal internal diameter of the left ventricle, determined by subtracting wall thickness from outer diameter for our hearts is 3.1 cm in systole and 5.6 cm in diastole (ratio 1:1.8), compared with an aortic valve diameter of 2 cm and a mitral valve diameter of 3 cm (ratio 1:1.5). The apex to base length of the left ventricular cavity averages 9.9 cm in systole and 10.7 cm in diastole (Table II). In the hearts studied average left ventricular volume decreased from 153 to 62 ml, which corresponds to an ejection fraction of 60 percent, a value not different from that determined in a number of studies. Substitution of the values for maximal left ventricular diameter, d, and the apex to base length, h, into the formula for the volume of a prolate hemispheroid, namely, $V = \pi/6\ d^2h$, we obtained 50 ml in systole (observed 62 ml) and 176 ml in diastole (observed 153 ml).

Right versus left ventricular topography: The form of the right ventricle is somewhat more difficult to characterize than the left. The inlet and outlet ports are separated and the cavity is largest beneath the larger inlet of the tricuspid valve and tapers to the diameter of the pulmonary valve outlet. Reduction of cavity size during systole depends mainly on the free wall because in the normal heart the interventricular septum functions as a portion of the left ventricular wall. The form of its wall appears to be further modeled by the external constraints of diaphragm and anterior chest wall as well as the distension of diastolic filling because there are usually two distinct segments of its wall joined at the acute margin. In a general way then both ventricles may be regarded as slightly bulbous tubes of a size similar to inlet and outlet ports and capable of systolic expulsion of a major part of their diastolic volume.

In conclusion, the cardiac ventricles may be considered as three conjoined segments of prolate spheroids. In diastole the ventricular configuration approximates a surface of minimal energy, that is, it has soap bubble-like behavior. The pressure-producing capacity of the ventricular segments correlates with their curvature-thickness indexes, a characteristic that may be susceptible to clinical determination with noninvasive techniques of study. The shape of the ventricle appears to correspond to that predicted by the principle of minimal work.

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Continuous Ventricular Dimensions in Man During Supine Exercise and Recovery

An Echocardiographic Study

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Ten healthy men aged 18 to 23 years performed supine bicycle ergometer exercise during continuous echocardiographic recording. Beat to beat analysis of ventricular dimensions revealed that during constant work load exercise end-diastolic dimension did not change and end-systolic dimension decreased insignificantly by 4 percent. The stroke dimension and fractional shortening of the ventricular dimension rose 7 and 5 percent, respectively. During recovery, end-diastolic dimension and stroke dimension increased above the resting value, beginning 26 seconds (range 16 to 45) after cessation of exercise, whereas heart rate fell promptly to resting levels by 37 seconds. The peak increase in end-diastolic dimension and stroke dimension averaged 11 and 35 percent, respectively. End-systolic dimension coincident with peak end-diastolic dimension decreased 11 percent in 6 of 10 subjects, and was unchanged in four. Fractional shortening of the ventricular dimension increased 8 percent ($P < 0.025$) in parallel with end-diastolic dimension.

These dimensional changes indicate a significant increase in end-diastolic dimension and stroke dimension in all 10 subjects during the recovery phase of supine exercise with a parallel rise in the percent shortening of the ventricular dimensions. During exercise a clear Frank-Starling effect is masked, whereas during recovery the continuing high level of venous return is dissociated from the decreasing heart rate, resulting in a transient increase in end-diastolic volume and a measurable Frank-Starling effect.

The response of the human left ventricle to exercise with respect to volume changes and dynamics of contraction is unresolved. The few studies in man have yielded variable and often conflicting data, perhaps in part because of variations in methodology and patient selection and failure to measure cardiac internal dimensions.

The echocardiogram defines the left septal and left ventricular posterior endocardial walls, and permits the noninvasive analysis of left ventricular internal dimensions. These measurements have been shown to correlate well with comparable dimensions determined angiographically.[1–3] The present investigation was undertaken to determine internal left ventricular dimensions during supine bicycle ergometer exercise and recovery in normal subjects. The echocardiogram was used to provide beat by beat measurements continuously during exercise and the unsteady state recovery period.

Methods

Subjects: Ten healthy volunteer male college students, aged 18 to 23 years, were studied. All had a normal cardiovascular history, physical examination and electrocardiogram at rest. Preliminary studies confirmed our ability to obtain technically excellent echocardiograms at rest and during exercise. The subjects

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were not conditioned to exercise by regular athletic programs.

Exercise protocol: Subjects were studied in the supine position at rest, during supine bicycle ergometric exercise and during recovery. Exercise was of 3 minutes' duration at a power output of 360 kg-m/min. The pedaling frequency was 60 revolutions/min, and a metronome was used to assist in regulating pedaling frequency. At the completion of the 3 minute exercise period, pedaling ceased abruptly. The feet remained on the pedals, 35 cm above the table, during the entire protocol.

Echocardiography: A Smith-Kline Ekoline-20A echocardiograph was interfaced with a Honeywell model 1856 fiberoptic strip chart recorder. An electrocardiogram was re-

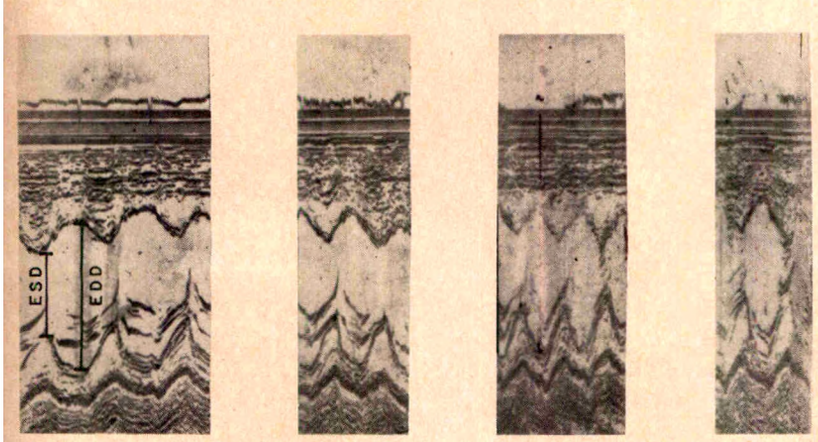


FIGURE 1. Case 10. Representative sections of the echocardiogram during supine bicycle exercise (300 kilopond-meters/min) in a representative subject. End-diastolic dimension (EDD) and end-systolic dimension (ESD) are drawn on the strip obtained during rest and listed, together with heart rate (HR), below each strip.

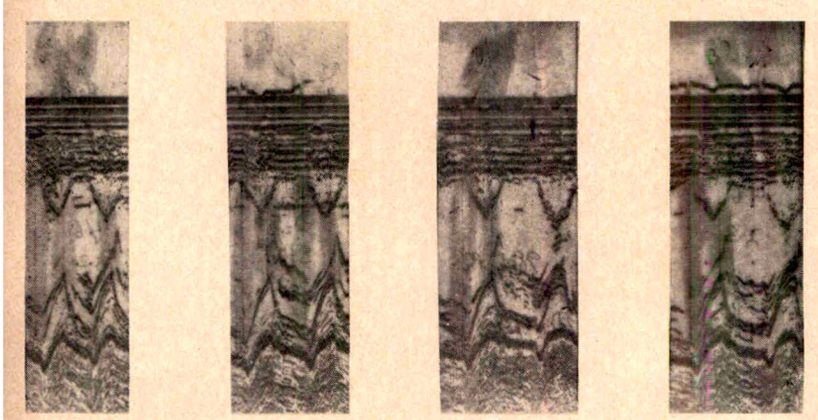


FIGURE 2. Case 10. Representative sections of the echocardiogram during recovery from exercise. The measured end-diastolic dimension (EDD), end-systolic dimension (ESD) and heart rate (HR.) are noted below each strip.

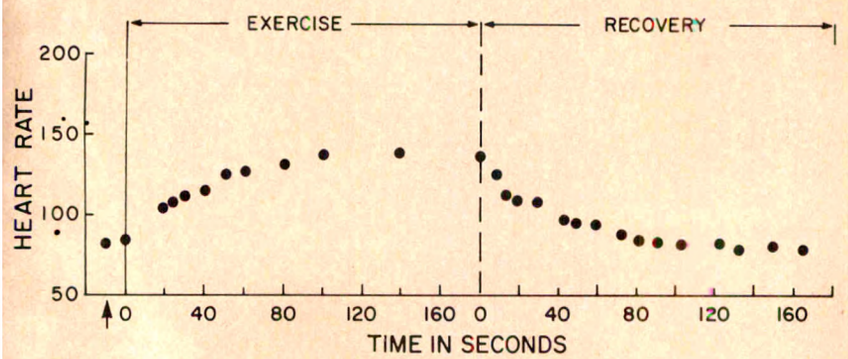


FIGURE 3. Case 10. Heart rate during supine exercise and recovery.

corded with the echocardiogram. The transducer, an SKI-Model C-14 (1/2 inch [1.27 cm], 2.25 megahertz, focused at 7.5 cm) was hand-held in the third or fourth intercostal space, affording the best simultaneous resolution of the septal and posterior wall endocardial echoes. Care was taken to hold the transducer perpendicular to the chest wall. Echocardiograms were used only if clearly defined simultaneous recordings of the left septal and posterior wall endocardial echoes were obtained at the tip of the mitral valve and remained unchanged throughout the study. Representative recordings during exercise and recovery are reproduced in Figures 1 and 2.

Measurements and calculations: *End-diastolic dimension:* measured at the terminal inscription of the QRS complex (Fig. 1).

End-systolic dimension: measured as the distance along a vertical line drawn from the peak upward motion of the posterior ventricular endocardium to its intersection on the septal endocardial echo.

Heart rate: measured from the recorded R-R interval.

Stroke dimension: calculated as the difference between end-diastolic and systolic dimensions of a given systole.

Fractional shortening of the ventricular dimension: Calculated as the stroke dimension divided by the end-diastolic dimension of a given systole.

A nasal thermistor was used during exercise, and measurements were not made during peak inspiration or expiration. The tracings were interpreted independently by two of us. In each case three cardiac cycles were measured, and the mean value used.

Results

Exercise (Table I): During supine exercise there was a mean increase in heart rate of 68.4 ± 11.4 percent (mean ± standard deviation) (Fig. 3). The end-diastolic dimension did not change significantly during exercise, and the end-systolic dimension decreased insignificantly (mean 2.6 percent, $P > 0.5$) (Fig. 4). The mean calculated stroke dimension increased by 6.2 ± 0.6 percent ($P > 0.05$) and the mean fractional shortening of the ventricular dimension by 5 ± 1.8 percent ($P > 0.05$) (Fig. 5). Four of the 10 subjects had an initial transient decrease in end-diastolic dimension during the initial 20 seconds of exercise that was not seen in the remaining 6 subjects.

Recovery (Table I): During recovery there was a significant increase in end-diastolic dimension in all 10 subjects (Fig. 6). The increase began 26 seconds into the recovery period (range 16 to 45 seconds) and was greatest a mean of 35 seconds into recovery (range 26 to 60 seconds). The end-diastolic dimension returned to baseline values by 90 seconds in all 10 subjects. When the peak end-diastolic dimension during recovery was compared with values at rest (which were not significantly different from exercise values), there was a significant increase by a mean value of 11.1 percent (range 8 to 16 percent).

TABLE I

Peak Percent Change in Ventricular Dimensions During Exercise and Recovery Compared With Resting Values

Case no.	EDD	ESD	SD	SD/EDD	HR
			A. During Exercise		
1	+4	+1	+4	+3	+69
2	−1	−6	+7	+4	+68
3	+1	+1	+4	+3	+48
4	−1	−7	+8	+5	+70
5	0	−1	+4	+4	+86
6	+4	0	+7	+8	+78
7	+5	+1	+8	+4	+75
8	−1	−10	+7	+6	+52
9	+4	0	+7	+5	+65
10	+3	−10	+7	+8	+73
Mean*	+0.8	−2.9	+6.2	+5	+68.4
	±2.4	±4.4	±1.6	± 1.8	±11.4
P	NS	NS	<0.05	<0.05	<0.01
			B. During Recovery		
1	+9	−10	+39	+11	+69
2	+14	−11	+37	+ 7	+68
3	+8	0	+27	+ 5	+48
4	+12	0	+29	+ 9	+70
5	+11	−7	+43	+11	+86
6	+10	−7	+29	+ 7	+78
7	+16	0	+37	+ 7	+75
8	+8	0	+29	+ 9	+52
9	+14	−17	+36	+ 8	+65
10	+9	−17	+45	+10	+73
Mean*	+11.1	−6.8	+35.1	+8.4	+68.4
	±2.8	±6.7	±6.3	±1.9	±11.4
P†	<0.01	NS	<0.025	<0.025	<0.01

* ± standard deviation.
† Paired analysis.
EDD = end-diastolic dimension; ESD = end-systolic dimension; HR = heart rate; SD = stroke dimension.

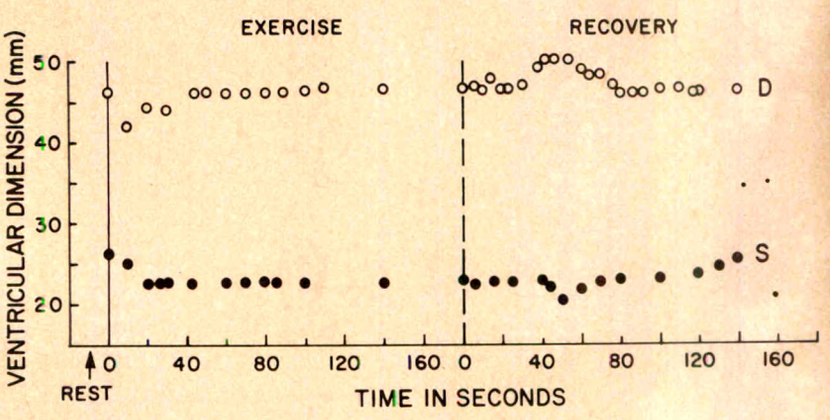


FIGURE 4. Case 10. Ventricular dimensions during supine exercise and recovery. End-diastolic dimension (D) is drawn as an **open circle** and end-systolic dimension (S) as a **closed circle.**

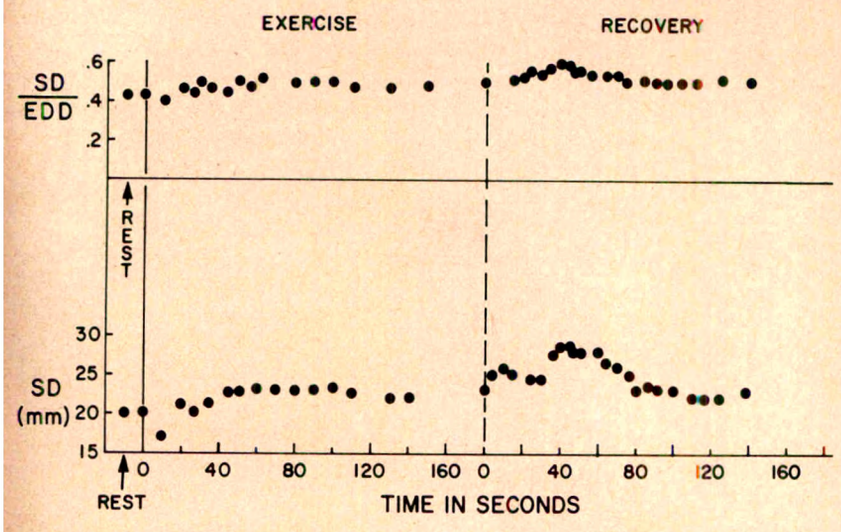


FIGURE 5. Case 10. Stroke dimension (SD) and fractional shortening of the ventricular dimension (SD/EDD) during supine exercise and recovery.

Changes in end-systolic dimension were inconsistent during recovery (Fig. 4). In 6 of the 10 subjects the end-systolic dimension decreased coincident with the increase in end-diastolic dimension, whereas in 4 subjects it remained unchanged from resting and exercise values. The stroke dimension and fractional shortening of the ventricular dimension increased in parallel with the end-diastolic dimension in all 10 subjects (mean increase 35.1 and 8.4 percent, respectively) (Fig. 5).

Discussion

Regulation of myocardial shortening in isolated tissues takes place either through alterations in contractility or through variation in initial fiber length of a muscle operating on the ascending limb of the length-tension curve. In the intact heart, similarly, either or both contractility and diastolic volume regulate the cardiac output, subject to the modulation and homeostatic influences of central and peripheral reflex activity affecting heart rate, peripheral vascular resistance and venous return. In the normal heart in the basal state, the ventricle is generally considered to be operating near the peak of the ascending limb of the length-tension curve. However, during the stress of exercise, the relative roles of changes in contractility and fiber length (that is, end-diastolic volume) in providing the increase in minute cardiac output are less clear. Previous studies in dogs have yielded conflicting data,

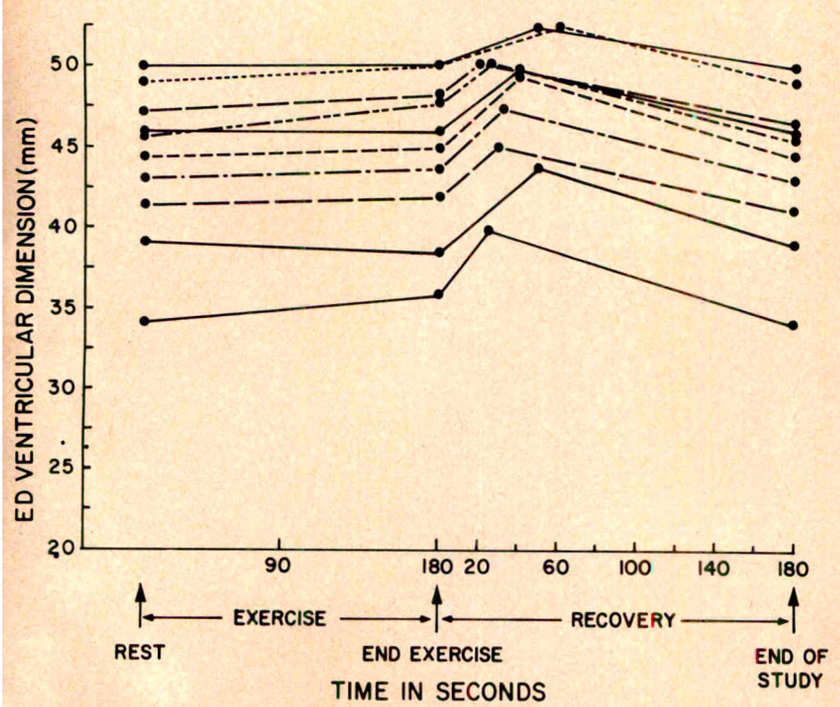


FIGURE 6. Cases 1 to 10. End-diastolic (ED) dimension at rest and at the end of exercise, the peak value during recovery and the value at 3 minutes of recovery.

in part because of variation in posture and anesthesia. In recent years, studies on conscious animals, made possible by technological improvements, have shown that end-diastolic dimension and stroke volume increase during moderate exercise. It was concluded that this represented in part the operation of the Frank-Starling mechanism.[4,5] These data conflict with the classic early studies of Rushmer.[6] He found no change in ventricular end-diastolic volume or stroke volume during exercise in conscious dogs and concluded that the Frank-Starling relation was not important in regulating cardiac output in the normal innervated heart.

Because differences in species, posture, reflex activity, heart rate response and pathologic states do not permit direct translation of data obtained in dogs to the human response, studies in man of the exercise response are important. However, most of the previous work in man has not included direct measurements of ventricular dimensions which define the role of contractility or length-tension changes. Gorlin et al.[7] found variable changes in end-diastolic volume using a thermodilution technique, which is subject to variable methodolgic error. Braunwald et al.[8] used epicardial markers and found a 3 to 5 percent decrease in end-diastolic and end-systolic dimensions and an increase in stroke dimension and in myocardial fiber velocity as measured by the slope of the volume-time curve of the ventricle.

Ventricular dimensions during exercise: Our study used the echocardiogram as a means of measuring left ventricular internal dimensions during exercise. Bowyer et al.[9] and Kraunz and Kennedy[10] have previously used the echocardiogram during exercise to examine left ventricular posterior wall motion alone. By studying subjects whose endocardial echoes were well defined for both the posterior wall and left septal surfaces, we were able to study chord or diameter dimensions during exercise, in both the steady state and the unsteady states of starting and stopping exercise. The data show a transient decrease in end-diastolic dimension in some but not all subjects on starting exercise, and a rapid return to baseline value during steady state exercise. Thus, no significant changes in end-diastolic or end-systolic dimensions were observed. However, the combination of small changes in end-diastolic or end-systolic dimension, or both, resulted in consistent increases in stroke dimension and percent shortening without demonstrating a Frank-Starling mechanism.

Ventricular dimensions during recovery from exercise: The analysis of ventricular dimensions during the recovery period proved rewarding. Of great interest is the observed transient increase in end-diastolic and stroke dimensions during the first 60 seconds of recovery from supine exercise (Fig. 6). This consistent finding can be explained by a continued high level of venous return due to assumption of the supine posture with slight leg elevation while the heart rate is rapidly decreasing (Fig. 3). The increased end-diastolic dimension reflects a Frank-Starling mechanism, superimposed on the continuing enhanced contractility as indicated by the increased fractional shortening of the ventricular dimension.

It would thus appear that during exercise, increases in ventricular dimensions are limited or masked by tachycardia and an increase in contractility. In recovery, the heart rate (and presumably contractility) appears to decrease faster than the metabolic demand and venous return, and thus the Frank-Starling mechanism is unmasked and end-diastolic dimension is increased. Vatner et al.[11] also noted that tachycardia masked increases in end-diastolic dimension during mild and moderate exercise in dogs and concluded that the Frank-Starling mechanism was not prominent during exercise of this degree. When they studied animals at the same heart rates at rest and during exercise, a clear Frank-Starling effect was observed.

Correlation with dye-dilution and angiographic studies: A previous study by Reindell et al.[12] postulated a transient increase in stroke volume during recovery from supine exercise on the basis of their findings of an increased pulse pressure and ratio of oxygen uptake to heart rate. Cumming[13] studied this problem directly, using serial dye-dilution determinations of cardiac output during the recovery phase from supine exercise. He reported an increase in stroke volume during recovery that was 36 percent over resting values in his male subjects. Our data are consistent with this finding, and because our study provided cardiac dimensions on a beat to beat basis, it reflected the magnitude and timing of this phenomenon more precisely than use of an indication-dilution method, which requires a steady state for validity.

Echocardiographic dimensions and the volumes derived from them have been shown in several studies to correlate well with comparable dimensions and volumes measured angiographically.[1–3] Redwood et al.[14] evaluated the ability of echocardiography to measure acute alterations in ventricular dimensions and volumes. They found it uniquely valuable in situations requiring noninvasive serial measurements, especially when nonuniformity of ventricular wall motion is not a concern, as in the normal subjects in our study. In our study we chose to deal only with the directly measured variable, linear dimension. Whether this dimension represents a true diameter or a chord of the left ventricular chamber, it is valuable as a constant internal cardiac landmark when recording serial changes. Calculation of volume from the linear dimensions, although subject to additional assumptions of constant geometry, yields directionally similar results.

Ventricular dimensions as index of contractility: We used changes in fractional shortening of the ventricular dimension as an index of contractility. However, alterations in ventricular afterload may also affect fractional shortening of the ventricular dimension (and ejection fraction) without implicating alterations in contractility. Thus the increased systemic pressure during exercise may have played a role in limiting possible extensive changes in fractional shortening of the ventricular dimension. In that case, however, afterload inhibition of shortening should have been associated with greater Frank-Starling effects during exercise (that is, increases in end-diastolic dimension). During the recovery phase, as blood pressure decreases, the effect

of afterload on the contractile response would diminish, minimizing a Frank-Starling effect. The converse was observed, suggesting that afterload was not instrumental in producing the sequential changes in fractional shortening of the ventricular and end-diastolic dimensions.

The degree of exercise in this study was mild (a work load of approximately 35 percent of the predicted maximum) to permit echocardiograms to be recorded without interference from respiration, and the patients were in the supine position. Technical problems did not permit echocardiographic analysis during upright exercise. The role of the Frank-Starling mechanism during more severe exercise in man is not known.

Clinical implication: The significance of this demonstrated increase in end-diastolic dimension during recovery from supine exercise can best be appreciated for the patient with ischemic heart disease. Wyatt et al.[15] demonstrated that an increase in preload of the canine left ventricle is associated with an increase in lactate production in a heart prepared with a partially occluded left anterior descending coronary artery. The clinical significance of this was noted by Ellestad,[16] who reported that the supine posture after exercise is frequently associated with an increase in S-T segment depression.

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Myocardial Structure and Function in Patients With Aortic Valve Disease and Their Relation to Postoperative Results

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Left ventricular angiographic studies were performed before and 6 months after aortic valve replacement with a Björk-Shiley prosthesis in 21 patients, 5 with aortic stenosis, 8 with mixed aortic valve lesions and 8 with aortic insufficiency. The degree of myocardial fibrosis and myocardial ultrastructural changes were evaluated from transmural needle biopsy specimens obtained from the left ventricular anterior free wall at operation. Twelve patients without heart disease served as control subjects for angiographic data. Patients with aortic valve disease had a significantly higher left ventricular mass before operation than control subjects and a lower ejection fraction and mean normalized systolic ejection rate. After operation left ventricular mass decreased considerably but did not reach normal level. Ejection fraction and mean normalized systolic ejection rate became normal in all patients with aortic valve disease. The percent fibrosis determined with morphometry was significantly higher in the subendocardium than in the subepicardium of pressure-overloaded hearts (predominant stenosis) (19 versus 13 percent) but equal in both layers of volume-overloaded hearts (predominant regurgitation) (19 versus 18 percent). Electron microscopy revealed significant intracell alterations of the nucleus, sarcomeres, mitochondria and cytoplasmic reticulum. When all patients, regardless of type of aortic valve lesion, were considered, there was no significant correlation before operation between percent fibrosis and ejection fraction (r 0.10) or mean normalized systolic ejection rate (r 0.02) but a significant inverse relation between left ventricular mass and ejection fraction (r 0.54) as well as mean normalized systolic ejection rate (r 0.49).

These data suggest that (1) Depressed left ventricular function in aortic valve disease is associated with ultrastructural degenerative cell changes, but complete recovery of cardiac function after aortic valve replacement is not prevented by these changes. (2) Interstitial myocardial fibrosis is not a primary determinant of depressed cardiac function in aortic valve disease.

The role of histopathologic myocardial changes in the regression of hypertrophy and recovery of cardiac function after removal of pressure or volume overload in man has not been defined.[1,2] It is generally accepted that in advanced left ventricular hypertrophy due to work overload interstitial myocardial fibrosis develops, probably as a result of focal cell destruction.[3–5] Recently, degenerative changes of myocardial cells associated with marked interstitial fibrosis have been described in aortic valve disease. These cell changes were considered responsible for impaired cardiac performance in some patients.[6,7] In a preliminary report we showed that the decrease in left ventricular function in aortic valve disease is correlated with the increase in left ventricular mass and with

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TABLE I

Clinical Data and Results of Morphologic Studies

Case no.	Age (yr) & Sex	Diagnosis	NYHA Class b	NYHA Class a	ECG RE Score b	ECG RE Score a	CT Ratio b	CT Ratio a	PPSG (mm Hg) b	PPSG (mm Hg) a	AR b	AR a	Months Postop at Second Study	Size of B-S Prosthesis	Point Counting: Tissue Samples (no.)	Point Counting: Percent Fibrosis Epi	Inter	Endo	Mean	EM
1	45M	AS	III	I	4	1	0.47	0.43	68	10	0	0	6	25	6	9	25	31	22	+
2	45M	AS	II	I	4	0	0.41	0.40	86	14	1	0	6	25	3	11	8	5	8	−
3	45M	AS	III	II	10	RBBB	0.56	0.52	69	—	1	—	—	—	3	14	12	24	17	−
4	59F	AS	III	I	4	0	0.52	0.47	76	—	1	—	—	—	5	13	8	21	14	+
5	45M	AS	III	—	RBBB	—	0.52	—	60	—	1	—	—	—	9	8	13	19	13	+
6	40M	AS + AI	III	II	8	2	0.58	0.45	188	28	2	0	5	23	7	4	16	10	10	+
7	50M	AS + AI	III	II	4	0	0.51	0.47	48	16	3	—	5	27	7	14	13	14	14	+
8	38M	AS + AI	III	I	9	0	0.64	0.42	64	8	5	0	5	27	3	—	16	—	16	+
9	61M	AS + AI	III	I	9	2	0.55	0.52	106	36	3	0	6	23	7	15	14	22	17	+
10	36M	AS + AI	IV	II	9	0	0.57	0.47	80	10	4	0	8	25	3	—	17	—	17	0
11	48M	AS + AI	III	—	1	—	0.54	—	42	—	3	—	—	—	5	17	20	21	19	+
12	43M	AS + AI	IV	—	8	—	0.73	—	48	—	5	—	—	—	3	28	22	20	23	−
13	37M	AS + AI	IV	II	10	1	0.69	0.57	52	—	5	—	—	—	7	11	18	24	18	+
14	19M	AI	III	I	5	2	0.57	0.56	0	24	5	0	11	27	4	23	17	—	20	+
15	50M	AI	III	II	RBBB	RBBB	0.53	0.50	12	4	4	0	5	29	3	30	—	13	22	+
16	63M	AI	III	I	RBBB	RBBB	0.56	0.56	0	2	3	0	5	29	5	25	18	11	18	−
17	25M	AI	III	I	3	0	0.39	0.36	0	0	3	0	6	27	3	—	15	—	15	−
18	26F	AI	III	II	1	0	0.49	0.48	0	40	3	0	7	25	9	12	5	6	8	+
19	44M	AI	III	II	6	3	0.56	0.49	0	6	3	1	6	27	5	33	8	20	20	+
20	16F	AI	III	I	4	0	0.50	0.50	0	—	4	—	—	—	3	7	—	20	14	0
21	35M	AI	III	I	7	2	0.47	0.37	16	—	4	—	—	—	4	5	21	35	20	−

− = data not obtained; + = present.

a and b = after and before operation, respectively; AI = aortic insufficiency; AR = aortic regurgitation determined angiographically; AS = aortic stenosis; B-S = Björk-Shiley; CT = cardiothoracic; EM = electron microscopy (sarcomere disorganization); ECG = electrocardiographic; Endo = subendocardial sample; Epi = subepicardial sample; Inter = intermediate sample; NYHA Class = New York Heart Association functional classification[9a]; Postop = postoperative; PPSG = peak to peak left ventricular to aortic systolic pressure gradient; RBBB = right bundle branch block; RE = Romhilt-Estes.

the presence of degenerative changes at the ultrastructural level.[8] In this study we quantitated the degree of interstitial myocardial fibrosis in biopsy material from patients who underwent aortic valve replacement. Electron microscopic studies of these tissue samples did not provide exact quantification of myocardial cell degeneration but allowed some qualitative estimation of ultrastructural alterations. The morphologic changes were then related to the pre- and postoperative hemodynamic data of these patients.

Methods

Patients: We studied 21 patients with isolated aortic valve disease between 2 and 6 weeks before aortic valve replacement. It was possible to restudy 13 of these patients 6.2 ± 1.7 (mean ± standard deviation) months (range 5 to 11 months) after aortic valve replacement by a Björk-Shiley tilting disc valve prosthesis. Patients 5, 11 and 12 (Table I) died in the early postoperative phase; five other patients refused the second investigation. Before operation, predominant aortic stenosis was found in 5 of the 21 patients, a mixed aortic valve lesion in 8 and predominant aortic insufficiency in the remaining 8. Associated mitral valve disease was excluded in all patients by analysis of synchronously registered left atrial and left ventricular pressure curves and, when necessary, additional angiographic studies of the left ventricle. Obstructive coronary artery disease was not found in any patient during selective coronary arteriography.

Functional class was estimated before and after operation by evaluating symptoms commonly associated with aortic valve disease: angina, syncope or presyncope and dyspnea. The electrocardiogram before and after operation was analyzed with the method of Romhilt and Estes[9] and cardiothoracic ratio was measured from the chest X-ray film preoperatively and at the time of restudy. Age, sex, diagnosis, functional class, Romhilt-Estes score, cardiothoracic ratio, aortic valve pressure gradient, degree of aortic regurgitation,[10] time after operation at second study and size of Björk-Shiley valve are listed for each patient in Table I.

Procedures: Patients with aortic valve disease were studied before and after operation without premedication in the same catheterization laboratory and with the same equipment. All patients were receiving digoxin before and after operation. A no. 8.5F Brockenbrough catheter was positioned in the left ventricle transseptally with use of a femoral vein puncture and a no. 8F pigtail catheter was inserted into the ascending aorta in retrograde fashion through the femoral artery. Before injection of contrast material, left ventricular and aortic pressures were measured with Statham P23Db pressure transducers and recorded on an Oscillomink direct writing system. The catheter manometer systems tested in vitro on a sine wave pressure generator had a uniform amplitude response up to 30 hertz. Single plane 35 mm cineangiograms of the left ventricle were filmed at a rate of 48 frames/sec in the 30° right anterior oblique projection after injection of 50 ml Urografin-76® into the left ventricle using a Brockenbrough catheter. Simultaneously the aortic pressure was recorded with a paper speed of 100 mm/sec. No mitral regurgitation was detected during this procedure during normally conducted sinus beats. In all patients aortic root angiography was performed to estimate the degree of aortic regurgitation.[10] Thereafter, coronary arteriography was carried out using the Judkins technique.

Calculations: From the cineangiograms silhouettes were drawn of the left ventricular cavity at end-diastole and end-systole. Where indentations in the ventricular outline were caused by papillary muscles, the outline was drawn to include all opacified areas. The long axis (L) of the left ventricle was taken as the longest measured line from the apex to the aortic valve. The minor axis (M) was calculated as $M = \pi \cdot A/4 \cdot L$, where A = area determined with planimetry. Ventricular volumes (V) were calculated using the single plane area-length method[11]: $V = \pi/6 \cdot M^2 \cdot L$. Correction factors for magnification and pincushion effect were obtained from a grid filmed in the plane occupied by the left ventricle. The regression equation of Kasser and Kennedy[11] was used. In 15 patients without heart disease we found no significant difference between stroke volume determined from manually checked cardiac output determinations obtained with the thermodilution technique[12] (no. 7F Swan-Ganz thermodilution catheter coupled to a cardiac output computer [Fa. Diefenbach, Ffm] and to a Kipp B12 direct writing system) and stroke volume assessed angiographically. Stroke volume assessed with thermodilution was 45.4 ± 10.8 ml/m^2 (mean ± standard deviation) compared with the angiographic value of 44.8 ± 10.2 ml/m^2. These values are in close agreement with the data reported by others[13] in normal persons.

A representative measurement of left ventricular wall thickness was made from the right anterior oblique projection of the ventriculogram in end-diastole at a point approximately midway between the apex and the aortic valve[14].

The ejection fraction was determined as stroke volume divided by end-diastolic volume times 100 percent. *The mean normalized systolic ejection rate* was calculated by division of ejection fraction by the ejection time as determined from the aortic pulse.

Left ventricular mass was calculated according to the method of Rackley et al.[15] as modified by Trenouth et al.[16] as: $V_M = (V_{C+W} - V') \cdot 1.05$, $V_{C+W} = 4/3\ \pi\ (M/2 + h)^2 \cdot (L/2 + h/2)$, where V_M = left ventricular mass, V_{C+W} = volume of left ventricular cavity plus wall, V' = end-diastolic volume, h = left ventricular wall thickness at the minor equator at end-diastole and 1.05 = density of the myocardium.

Collection and preparation of biopsy tissues: Tissues were obtained by biopsy from each patient at the time of open heart surgery. Operation was performed with the patient on cardiopulmonary bypass, utilizing a disposable bubble-type oxygenator. We use a Tru-cut biopsy needle (Travenol Laboratories) to take a transmural biopsy specimen from the left ventricular anterior free wall. The specimen was taken before cross-clamping of the aorta from the beating heart. In three patients (Cases 8, 10 and 17) only an intramural biopsy specimen was obtained. Immediately after biopsy the tissues were separated into subepicardial, intramural and subendocardial samples and were fixed in buffered 6 percent glutaraldehyde. Most patients had more than one biopsy specimen (Table I). After immersion fixation for 24 hours at 4° C the samples were rinsed in 0.1 molar cacodylate buffered with 7.5 percent sucrose during 12 hours at 4° C. After postfixation for 1 hour in 2 percent osmium tetroxide in veronal acetate buffer at pH 7.4 with 4 percent sucrose at 4° C, the tissues were dehydrated in graded series of alcohol, treated with propylene oxide and embedded in Epon®. After polymerization semithin sections of 1 to 2 μm thickness were prepared and stained with alkaline toluidine blue for light microscopy. Each block measured 1 to 4 mm^2 in area.

Morphometry was carried out with the light microscope using a special grid with vertical and horizontal lines providing 110 intersections (points). According to the basic principles of morphometry,[17] counting of the number of points overlying a structure results in a quantitative determination of the volume of the structure in relation to the volume of the entire

TABLE II

Hemodynamic Data

Case (no.)	Before Operation: HR (beats/min)	LVSP (mm Hg)	LVEDP (mm Hg)	EDVI (ml/m²)	EF (%)	MNSER (ed vol/sec)	LVMI (g/m²)	Fibrosis %	Fibrosis Mass (g/m²)	LVMMI (g/m²)	After Operation: HR (beats/min)	LVSP (mm Hg)	LVEDP (mm Hg)	EDVI (ml/m²)	EF (%)	MNSER (ed vol/sec)	LVMI (g/m²)
Aortic Stenosis																	
1	86	180	22	92	73	2.80	240	22	52.8	187.2	75	120	10	51	75	3.13	173
2	72	184	28	72	59	1.82	142	8	11.4	130.6	83	125	20	64	71	2.84	82
3	67	208	19	106	58	1.76	198	17	33.6	164.4	...	...	...	...	...	...	...
4	83	224	25	89	47	1.32	193	14	27.0	166.0	...	...	...	...	...	...	...
5	AF	180	22	...	...	...	132	13	17.2	114.8	...	...	...	...	...	...	...
Mean	77	195	23	90	59.3	1.93	181				79	123	15	58	73	2.99	128
± SD	9	20	3	14	10.7	0.62	44				6	4	7	9	2.8	0.21	64
P value	NS	<0.001	<0.001	NS	NS	NS	<0.01				...	...	...	...	...	...	...
Aortic Stenosis + Aortic Insufficiency																	
6	74	296	33	130	42	1.24	257	10	25.7	231.3	75	148	14	74	88	3.14	146
7	75	208	32	132	65	2.32	203	14	28.4	174.6	77	136	11	107	72	2.88	155
8	98	168	41	210	36	1.33	325	16	52.0	273.0	92	136	9	61	70	2.92	144
9	77	204	22	158	53	1.51	236	17	40.1	195.9	77	156	12	98	68	2.23	179
10	88	168	32	202	22	0.87	271	17	46.1	224.9	75	148	9	68	68	2.19	123
11	68	196	23	112	60	2.00	165	19	31.4	133.6	...	...	...	...	...	...	...
12	91	144	38	263	21	0.60	291	23	66.9	224.1	...	...	...	...	...	...	...
13	97	172	28	227	21	0.70	288	18	51.8	236.2	...	...	...	...	...	...	...
Mean	84	195	31	179	400	1.32	255				79	145	11	82	73.2	2.67	149
± SD	11	46	7	54	17.9	0.61	52				7	9	2	20	8.4	0.43	20
P Value	NS	<0.01	<0.001	<0.001	<0.01	<0.01	<0.001				NS	<0.01	NS	NS	NS	NS	<0.001
Aortic Insufficiency																	
14	67	146	23	228	63	1.85	268	20	53.6	214.4	86	136	6	73	68	2.52	154
15	67	160	11	146	52	1.93	264	22	58.1	205.9	80	152	14	132	63	2.17	195
16	83	160	15	167	42	1.56	184	18	33.1	150.9	90	184	10	91	55	2.08	143
17	77	120	15	139	54	1.59	187	15	28.1	158.9	75	120	11	89	56	1.87	142
18	113	152	20	169	57	2.04	123	8	9.8	113.2	110	172	8	71	64	2.29	107
19	65	128	9	170	61	2.26	191	22	38.2	152.8	67	120	14	125	72	2.67	136
20	90	152	6	153	51	1.89	157	14	21.9	135.1	...	...	...	...	...	...	...
21	102	166	28	143	47	1.57	172	20	34.4	137.6	...	...	...	...	...	...	...
Mean	83	148	16	164	53.4	1.84	193				85	147	11	97	63.0	2.27	146
± SD	18	16	7	28	6.9	0.25	50				15	27	3	26	6.6	0.29	29
P value	NS	<0.01	NS	<0.001	<0.001	<0.01	<0.001				NS	NS	NS	NS	NS	NS	<0.01
Normal Subjects																	
Mean	75	122	11	79	68.3	2.31	85	...	...	...	75	122	11	79	68.3	2.31	85
± SD	12	15	3	21	6.6	0.30	16	...	...	...	12	15	3	21	6.6	0.30	16

– = data not obtained.

AF = atrial fibrillation; EDVI = end-diastolic volume index; ed vol = end-diastolic volume; EF = ejection fraction; Fib. = fibrosis; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular systolic pressure; LVMI = left ventricular mass index; LVMMI = left ventricular muscle mass index; MNSER = mean normalized systolic ejection rate; NS = not significant; *P* = probability (values compared with those of normal subjects); SD = standard deviation.

tissue under the square grid. Therefore, the total number of points was regarded as 100 percent and the points counted in the fibrotic area were expressed as the percent of the entire tissue within the limits of the grid. In this investigation all points overlying fibrotic tissue were determined. The axis of the square grid was then rotated about 45°, and determination of the points was repeated. After a random sampling procedure a different part of the same section was chosen and the points overlying the fibrotic area were counted with the grid in control position and after rotation of 45°. In this way, two areas of each section were counted twice. Only longitudinal sections at a magnification of 250× were evaluated, and blood vessels and perivascular interstitial cells were excluded from the fibrotic area. In each patient three to nine tissue samples and two sections from each sample were counted. For electron microscopic examination thin sections were cut with a LKB Ultratome III, mounted on uncoated copper grids, stained with saturated uranyl acetate and lead citrate and examined with a Philips electron microscope 300.

Results

Clinical data: All patients with aortic valve disease showed improvement in functional class and the Romhilt-Estes-score. The cardiothoracic ratio improved in all but Patient 16, who had no reduction of cardiothoracic ratio (Table I). The greatest reduction of cardiothoracic ratio (from 0.64 to 0.42) occurred in Patient 8, who had mixed aortic valve disease.

Hemodynamic data: *Before operation,* patients with aortic stenosis had increased left ventricular systolic and end-diastolic pressures ($P < 0.001$ compared with control values), normal values for end-diastolic volume, ejection fraction and mean normalized systolic ejection rate ($P > 0.05$) but an increased left ventricular mass (213 percent of control value, $P < 0.001$, Table II). Patients with both aortic stenosis and insufficiency had increased left ventricular systolic and end-diastolic pressures ($P < 0.01$ and $P < 0.001$) and end-diastolic volume ($P < 0.001$) with a reduced ejection fraction ($P < 0.01$) and mean normalized systolic ejection rate ($P < 0.01$). Left ventricular mass was increased to 300 percent of control value ($P < 0.001$). Patients with aortic insufficiency had increased left ventricular systolic pressure ($P < 0.01$) but a normal left ventricular end-diastolic pressure ($P > 0.05$). End-diastolic volume was increased ($P < 0.001$), and ejection fraction ($P < 0.001$) and mean normalized systolic ejection rate ($P < 0.01$) were decreased (Table II). Left ventricular mass was increased (227 percent of control value, $P < 0.001$).

The two patients with aortic stenosis who were restudied postoperatively showed a reduction of left ventricular systolic pressure from 180 and 184 to 120 and 126 mm Hg, respectively. Left ventricular end-diastolic pressure and volume decreased in both patients. Whereas left ventricular mass decreased considerably, an increase in ejection fraction and mean normalized systolic ejection rate was noted. Paired data before and after operation in five patients with mixed aortic valve disease showed at comparable heart rates ($P > 0.05$) a significant decrease of left ventricular systolic pressure ($P < 0.05$) and end-diastolic pressure ($P < 0.01$). End-diastolic volume ($P < 0.05$) and left ventricular mass decreased ($P < 0.05$), whereas ejection fraction ($P < 0.05$) and mean normalized systolic ejection rate ($P < 0.01$) improved.

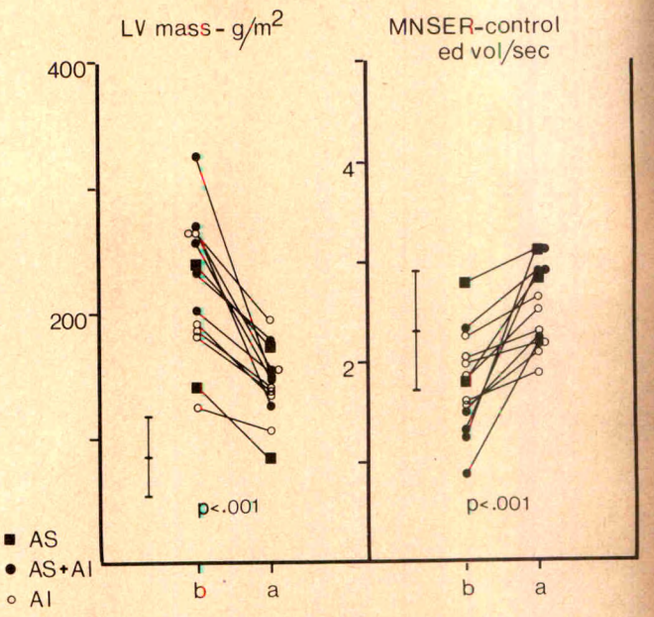


FIGURE 1. Individual data on left ventricular (LV) mass and mean normalized systolic ejection rate (MNSER) before and after aortic valve replacement in patients with aortic valve disease. The normal range is indicated by **vertical bars** (mean value ±2 standard deviations). a and b = after surgery and before operation, respectively; AI = aortic insufficiency; AS = aortic stenosis; AS + AI = aortic stenosis plus aortic insufficiency; ed vol = end-diastolic volume.

The six patients with aortic insufficiency had no further evidence of significant aortic regurgitation after operation (Table I). At comparable heart rates left ventricular systolic pressure was unchanged ($P > 0.05$) as was left ventricular end-diastolic pressure. Left ventricular end-diastolic volume and left ventricular mass decreased significantly whereas ejection fraction and mean normalized systolic ejection rate increased ($P < 0.01$).

Figure 1 illustrates the regression of left ventricular mass and the increase of mean normalized systolic ejection rate after operation, indicating improved cardiac function after aortic valve replacement. When we considered all patients regardless of the type of aortic valve lesion, we found a significant inverse relation between left ventricular mass and ejection fraction (r 0.54, $P < 0.05$) and between left ventricular mass and mean normalized systolic ejection rate (r 0.49, $P < 0.05$) before operation but not after operation (r 0.00 and r 0.06, $P > 0.05$).

Myocardial fibrosis: Table I presents the results of evaluation of interstitial fibrosis, and Figures 2 and 3 show representative examples of light micrographs. Table I presents the average percent fibrosis for the subepicardial, intramural and subendocardial muscle layers. The overall mean value was calculated by averaging the mean values obtained for the different layers. Between three and nine tissue samples were used to

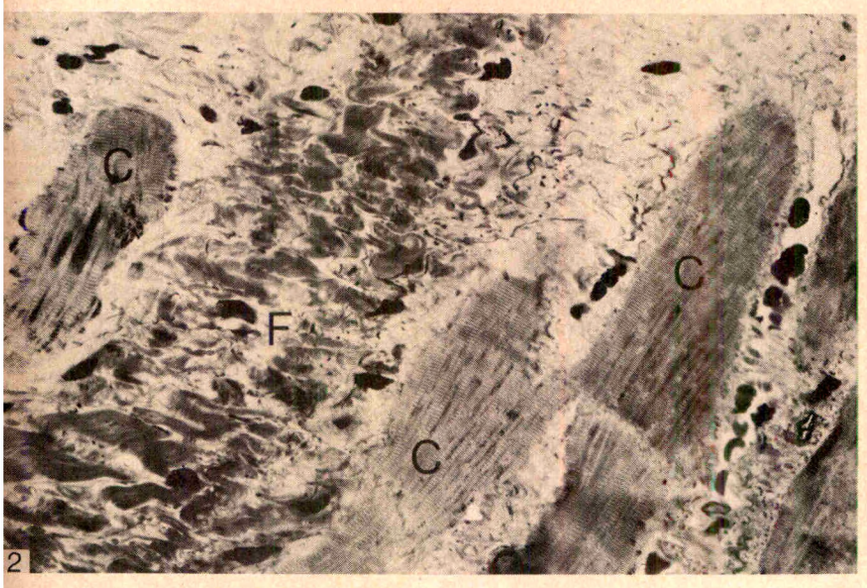


FIGURE 2. Light micrograph of subendocardial tissue from a patient with aortic stenosis. The cardiac muscle cells (C) have lost their interconnections, and large amounts of interstitial fibrosis (F) are evident (×1,250, reduced by 34 percent).

calculate the percent fibrosis, because fibrosis in hypertrophied hearts is widespread but may be focally accentuated.[5] In patients with predominant pressure overload (aortic stenosis and aortic stenosis plus insufficiency) the percent fibrosis was significantly larger in the subendocardium than in the subepicardium (19 versus 13 percent, $P < 0.05$). In the group with predominant volume overload (aortic insufficiency) there was no significant difference between percent fibrosis of both layers (19 versus 18 percent, $P > 0.05$).

We calculated total left ventricular fibrotic mass by multiplying the mean percent fibrosis and left ventricular mass (divided by 100 percent). Left ventricular muscle mass was then determined as left ventricular mass minus left ventricular fibrotic mass. Figure 4 shows the relation between left ventricular fibrotic mass and left ventricular muscle mass for all patients studied. This relation is significant and has a correlation coefficient of 0.76 ($P < 0.001$). However, there was no significant correlation between percent fibrosis and ejection fraction (r 0.10, $P > 0.05$) or mean normalized systolic ejection rate (r 0.02, $P > 0.05$) when all cases were considered irrespective of type of aortic valve lesion.

Myocardial ultrastructure: Electron microscopy, performed in 15 patients (Table I), revealed features of degeneration of the cardiac muscle cells in 13 patients and their absence in Patients 10 and 20. The morphologic alterations interpreted as degenerative were found in all layers of the myocardium. There appeared to be no correlation between the nature of the hemodynamic alterations to play no role and the presence of these changes (Table I). The degenerative alterations consisted of (1) unusually large nuclei exhibiting invagination of the nuclear membrane, irregular distribution of chromatin and the occurrence of tubular nuclear structures; (2) loss of myofibrils and accumulation of Z band material; (3) accumulation of large amounts of mitochondria exhibiting variable shape and

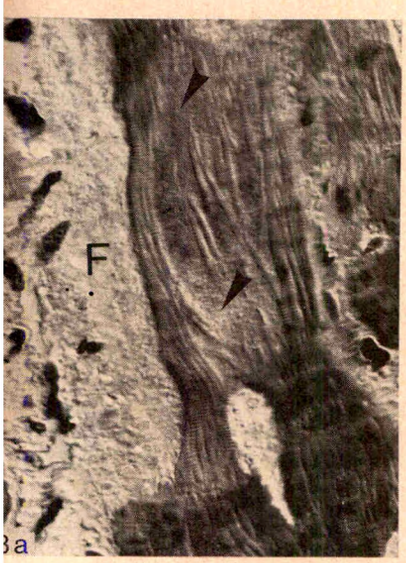




FIGURE 3. Light micrographs. **a,** a myocardial cell showing areas free of contractile elements **(arrowheads)**. Increased amounts of interstitial fibrosis (F) are shown close to the cell (×1,250, reduced by 35 percent; Normarski optics). **b,** myocardial cells showing loss of myofilaments **(arrowheads)**. There are many palely stained areas of cytoplasm in which myofibrils appear to be absent (×1,250, reduced by 35 percent).

size; (4) occurrence of large cytoplasmic areas that were devoid of contractile material but filled with glycogen, ribosomes, and sometimes increased amounts of sarcoplasmic reticulum; and (5) presence of proliferative fibroplasts, macrophages, mast cells, and increased amounts of collagen fibers in the interstitial space.

Figures 4 to 7 show the typical features of myocardial cells with loss of contractile material and disturbed sarcomeric organization. No attempt was made to correlate the frequency and degree of myocardial cell degeneration with cardiac function. In all 13 patients these ultrastructural alterations were relatively consistent, and we believed that quantitative estimation or grading of degenerative changes would be a subjective procedure.

Discussion

Critique of methods: Our study was designed to determine the significance of interstitial myocardial fibrosis and degenerative cell changes in postoperative cardiac function in patients with aortic valve disease. The transmural biopsy technique under direct vision when previously used in patients with coronary artery disease[18] was found to be of considerable accuracy when related to electrocardiographic findings and ventricular asynergy in the same region. We tried to minimize the sampling error by taking more than one biopsy specimen in most patients. In addition there is evidence that in left ventricular hypertrophy the fibrotic process and the degenerative cell changes are widespread but not localized.[4,5] The presence of increased amounts of interstitial myocardial fibrosis in advanced hypertrophy due to aortic valve disease is well known.[3,4,5,19,20] Reichenbach et al.[5], in a preliminary study of 10 patients with mitral and aortic valve disease but without coronary heart disease, found, a correlation between

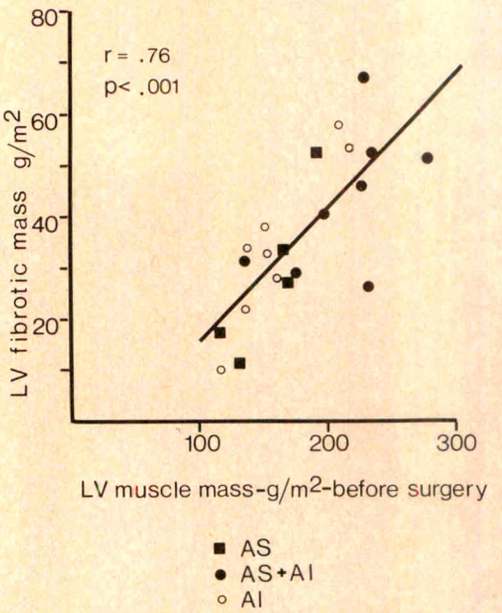


FIGURE 4. Linear relation between left ventricular (LV) muscle mass before operation and left ventricular fibrotic mass as determined with morphometry. AI = aortic insufficiency; AS = aortic stenosis; AS + AI = aortic stenosis plus insufficiency; p = probability.

fibrosis and left ventricular mass. More severe fibrosis was found in aortic than in mitral valve disease and fibrosis tended to be more prominent in the subendocardial area. Sasaki et al.[21] found a correlation between the amount of fibrosis and increased heart weight in a morphometric study of hypertrophied hearts. The good correlation between mass of fibrosis and left ventricular muscle mass in our biopsy specimens confirms these

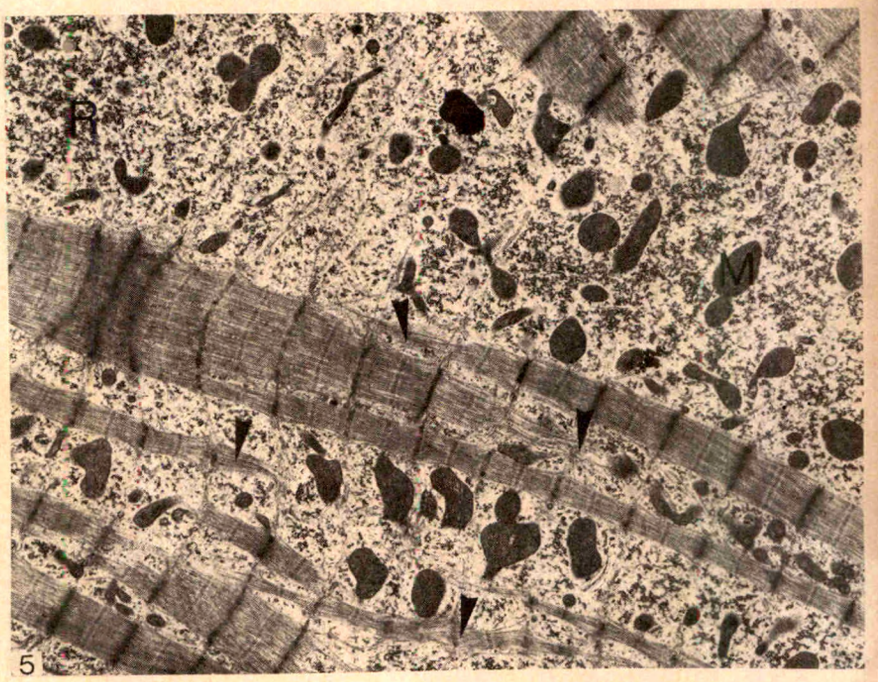


FIGURE 5. Electron micrograph of a myocardial cell with severe disturbance of the regular arrangement of sarcomeric units. The areas devoid of contractile material contain mitochondria (M), glycogen and free ribosomes (R). The myofilaments show fragmentations **(arrowheads)** (×9,900, reduced by 32 percent).

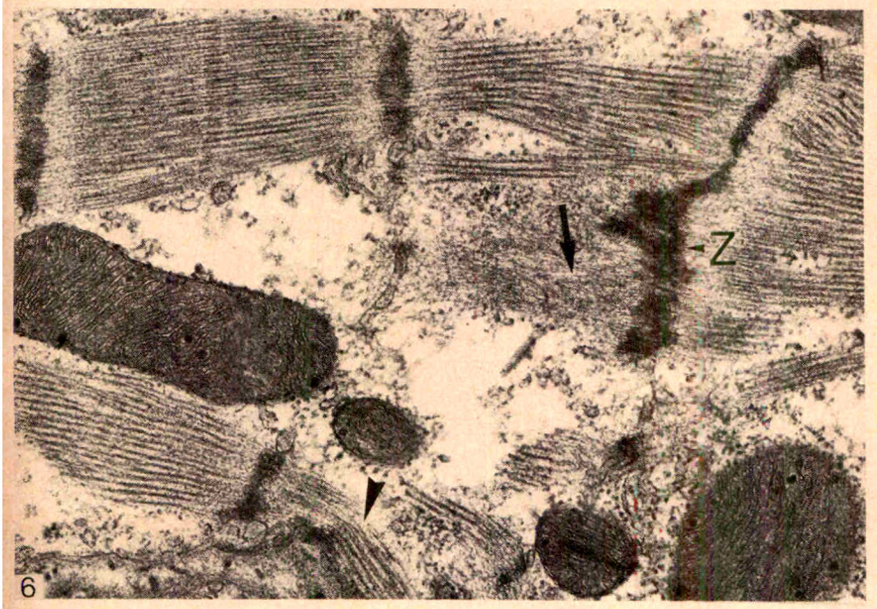


FIGURE 6. Electron micrograph of the contractile elements in a hypertrophied myocardial cell. The myofilaments are irregularly arranged, running in different directions **(arrowhead)**. The Z band (Z) is thickened and irregular. Thick filaments are lost near the abnormal Z band leaving thin filaments **(arrow)** (×56,000, reduced by 34 percent).

reports. Furthermore it demonstrates that our biopsy technique allows the evaluation of the morphologic state of the myocardium within a fair range of accuracy. Although objective quantification of ultrastructural changes in myocardial cells is not possible with our technique, degree of qualitative evaluation can be obtained. We accepted degenerative changes of the myocardium as significant when they were found in the majority of tissue samples.

To assess cardiac function in normal and hypertrophied hearts we used the ejection fraction and the mean normalized systolic ejection rate. The ejection phase indexes express function per unit of muscle and are considered useful in detecting changes in level of inotropic state.[22] Furthermore, others[23] have shown that the ejection phase indexes are superior to isovolumetric indexes in detecting depressed myocardial function in the basal state.

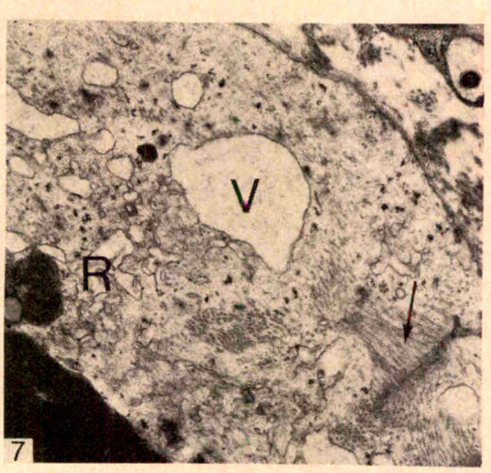


FIGURE 7. Electron micrograph showing large vacuoles (V) and tubular and vesicular sarcoplasmic reticulum (R). The cell can be identified as a cardiac muscle cell because some remnants of myofilaments **(arrows)** can be detected (×16,800, reduced by 32 percent).

Regression of hypertrophy and recovery of left ventricular function after operation. After aortic valve replacement there were significant reductions in left ventricular mass and left ventricular end-diastolic volume. However, whereas end-diastolic volume became fully normal, left ventricular mass did not. In addition, the decreased left ventricular function, as evaluated with ejection phase indexes, was reversible and became normal in patients with aortic valve disease. The improvement in cardiothoracic ratio, Romhilt-Estes score and symptoms correlates well with the angiographic data. It is well known that in hypertrophied hearts left ventricular function may be normal at rest but abnormal during stress.[24] This fact may limit the significance of our results but it does not alter our finding that resting cardiac function improved considerably after aortic valve replacement. Another recent investigation in this laboratory[25] evaluated a series of patients with aortic valve disease after aortic valve replacement at rest and during isoproterenol-induced stress using two ventricular angiograms. After aortic valve replacement most patients had a normal ejection fraction during isoproterenol stress although a peak transvalve pressure gradient of 30 to 40 mm Hg developed.

We believe that the persisting mild outflow tract obstruction after implantation of a Björk-Shiley prosthesis prevents complete regression of left ventricular hypertrophy. Reductions in end-diastolic volume and left ventricular mass after homograft aortic valve replacement were reported.[26] Normal cardiac function after aortic valve replacement by a Starr-Edwards prosthesis was observed by Hultgren et al.,[27] who found the greatest decrease of heart size in patients with heart failure before operation. Recently Schuler et al.[28] described an important influence of time on recovery of myocardial function after valve replacement for aortic insufficiency. In our study this time factor may not have

played an important role because the data were obtained 5 to 8 months postoperatively in 12 of 13 patients.

Relation between myocardial structure and postoperative result: Before operation, left ventricular function was significantly reduced in patients with aortic valve disease. This reduced function was dependent upon the degree of hypertrophy of the myocardium but did not correlate significantly with percent fibrosis. These findings suggest that the scars thought to have a detrimental effect on contraction, that is, separation of cardiac muscle cells and disruption of the functional myocardial syncytium,[3,29] are less important for overall cardiac performance. The ultrastructural myocardial alterations found in most cases are probably more related to the reduced contractile function in these hearts. Our results imply that these alterations were the cause of the reduced contractile function in our patients. Such structural alterations were previously described in detail in a similar group of patients by Maron et al.,[6,7] who suggested that degenerative changes in myocardial cells may explain the impaired cardiac function in patients with aortic valve disease. Although we could not correlate the degree of cell degeneration with cardiac function, we did show that the "myocardial factor" was present in patients with depressed cardiac function and advanced hypertrophy.

Restudy of the same patients 6 months after aortic valve replacement allowed comparison of preoperative morphologic features and functional state of the myocardium with the postoperative clinical and hemodynamic course. Obviously the presence of cardiac muscle cell degeneration was not associated with a lack of improvement after operation. Six months postoperatively left ventricular hemodynamics at rest were restored to normal even in patients with severe myocardial fibrosis and muscle cell degeneration.

Implications: We conclude that the preoperative depressed cardiac function in patients with aortic valve disease is related to ultrastructural myocardial changes and not to degree of myocardial fibrosis. The restoration of depressed myocardial function after aortic valve replacement strongly suggests that the ultrastructural myocardial changes described are fully reversible. The generally accepted term "degenerative" is probably not adequate.

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Diagnostic Value of Exercise-Induced S-T Segment Depression In Patients With Right Bundle Branch Block

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The sensitivity of submaximal exercise testing in detecting coronary artery disease in patients with right bundle branch block is not known. Thirty patients were identified who had right bundle branch block, submaximal treadmill exercise tests and selective coronary angiography. Eighteen of these patients were found to have significant coronary artery disease. Treadmill exercise testing was associated with S-T segment depression limited to leads V_1 to V_3 in three patients with coronary artery disease, whereas S-T segment depression was noted in leads V_4 to V_6 in eight patients, all of whom had multivessel coronary artery disease. Among patients without significant coronary artery disease, six had S-T segment depression limited to leads V_1 to V_3 during exercise testing.

In this patient population, composed predominantly of men with symptoms of ischemic heart disease, the 12 lead submaximal treadmill exercise test had a sensitivity rate of 69 percent and a specificity rate of 45 percent in detecting coronary artery disease in the presence of right bundle branch block. The specificity of the treadmill test appears to be greater if S-T depression is recorded in leads V_4 to V_6. S-T segment depression limited to leads V_1 to V_3 often represents a false positive exercise test.

The sensitivity of submaximal treadmill exercise testing in detecting coronary artery disease in patients with right bundle branch block is not known. Recently, Whinnery et al.[1] found that none of 40 asymptomatic apparently healthy men with acquired right bundle branch block had abnormal S-T segment changes in response to maximal treadmill testing. All of the patients had cardiac catheterization, and eight were found to have significant coronary artery disease. Six of the eight had only single vessel disease. The authors concluded that the specificity of the exercise treadmill test was excellent in patients with right bundle branch block because there were no false positive responses, but they could not determine the sensitivity because no test was positive. Our study was designed to evaluate the sensitivity and specificity of submaximal treadmill exercise testing in detecting coronary artery disease in patients with right bundle branch block, all of whom had symptoms of ischemic heart disease.

Methods

Patients: A chart review was undertaken at this medical center, and all 30 patients who had evidence of right bundle branch block in the resting electrocardiogram and who had coronary angiography and a 12 lead submaximal exercise treadmill test were included. No patient was receiving digoxin at the time of study; two were taking propranolol and one hydrochlorothiazide.

The mean age of the patients was 54 years (median 58; range 30 to 69). There were 27 men and 3 women. Treadmill exercise tests were performed to evaluate chest pain in 25 patients, arm pain in 1 patient and exercise tolerance after a history of myocardial infarction in 3 patients and to clarify unexplained shortness of breath in one patient.

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TABLE I

Treadmill Exercise Test Results in 19 Patients With Normal Coronary Angiography or With Single Vessel Coronary Artery Disease

Coronary Artery Involved	Exercise Test			
	Nondiagnostic	Negative	Positive V_1 to V_3	Positive V_4 to V_6
None	1M	5M	6M	0
LAD	1M	1F	2(1M;1F)	0
LCx	0	1M	0	0
Right	0	2M	0	0

F = female; LAD = left anterior descending; LCx = left circumflex; M = male.

TABLE II

Treadmill Exercise Test Results in Patients With Double Vessel and Triple Vessel Coronary Artery Disease

Coronary Arteries Involved	Exercise Test			
	Nondiagnostic	Negative	Positive V_1 to V_3	Positive V_4 to V_6
LAD + LCx	0	1M	1M	0
LAD + right	0	0	0	3M
LAD + LCx + right	1M	0	0	5 (4M; 1F)

F = female; LAD = left anterior descending; LCx = left circumflex; M = male.

TABLE III

Summary of Treadmill Exercise Test Results in Patients With and Without Coronary Artery Disease

	Nondiagnostic	Negative	Positive V_1 to V_3	Positive V_4 to V_6
Coronary artery disease	2	5	3	8
No coronary artery disease	1	5	6	0
Total	3	10	9	8

Exercise testing: All patients had a multistage treadmill exercise test using the Bruce protocol,[2] modified to include a Stage 0 (0 percent grade; 1.7 miles/hour). Silver-plated fluid column adhesive electrodes were used, and the chest electrodes were placed in the standard positions. The skin was prepared by first cleansing with alcohol and then abrading with silicone carbide 220 paper to reduce electrode resistance. Twelve lead electrocardiograms were recorded on either a Hewlett-Packard or Siemens three channel recorder. Both recorders have a frequency response that exceeds the American Heart Association's requirement of 0.05 to 100 hertz for diagnostic electrocardiography. Electrocardiograms were obtained before exercise with the patients supine and standing, after each 3 minutes of exercise and in the supine position every 2 minutes for 10 minutes after exercise.

Leads V_4 to V_6 were monitored continuously during the exercise test. Indirect cuff blood pressure measurements were obtained after completion of each recording. Patients exercised until they achieved 90 percent of their predicted maximal heart rate or manifested symptoms of angina or severe fatigue. All exercise tests were interpreted by the same cardiologist (T.T.). A positive exercise test was defined as one showing at least 1 mm of flat or downsloping S-T segment depression from the baseline that persisted for at least 0.08 second before returning to baseline. In the absence of a positive S-T segment response, the exercise test was considered nondiagnostic if the peak heart rate achieved was less than 90 percent of the predicted maximum.

Coronary angiography: Each patient had cardiac catheterization performed. Injections of both the right and left coronary arteries were performed in multiple views and recorded on 35 mm cine film. The coronary angiograms were reviewed by two cardiologists and agreement was reached on the severity of each lesion. Significant coronary artery disease was defined as 70 percent or greater narrowing of the cross-sectional diameter of one or more coronary arteries.

Results

Normal coronary arteriograms (Table I): Twelve patients had normal coronary arteriograms. All 12 had been evaluated for chest pain, arm pain or unexplained shortness of breath or to determine exercise tolerance after a history of a prior myocardial infarction. The resting electrocardiograms from these patients could not be interpreted as showing a myocardial infarction. No S-T segment depression was noted in leads V_4 to V_6 during the exercise test in any patient. The six patients with a positive exercise test had S-T segment depression limited to leads V_1 to V_3.

Single vessel coronary disease (Table I): Seven patients had single vessel coronary artery disease. The left anterior descending coronary artery was involved in four patients, the right coronary artery in two patients and the circumflex coronary artery in one patient. Each patient in this group was evaluated for symptoms of chest pain. Two patients had a positive treadmill exercise test with S-T depression limited to leads V_1 to V_3. One patient had a nondiagnostic exercise test. No patient in this group had S-T depression in leads V_4 to V_6 during the exercise test.

Double and triple vessel disease (Table II): Five patients had two vessel coronary artery disease. All had involvement of the left anterior descending coronary artery. Three patients also had disease in the right and two also in the circumflex coronary artery. Each patient in this group was evaluated for chest pain. The three patients with lesions of both the left anterior descending and right coronary arteries had a positive treadmill exercise test with S-T depression in leads V_4 to V_6. One patient with disease in both the left anterior descending and circumflex coronary arteries had a positive exercise test with S-T depression limited to leads V_1 to V_3.

Six patients had triple vessel coronary artery disease. Each patient in this group was evaluated for chest pain. Five patients had a positive treadmill exercise test with S-T depression noted in leads V_4 to V_6. There were no positive exercise tests with S-T depression limited to leads V_1 to V_3. One patient had a nondiagnostic exercise test.

Summary of treadmill exercise tests (Table III): Eighteen of the 30 patients were found to have significant coronary artery disease, and 11 of these had a positive treadmill exercise test. Eight of the 11 patients

had S-T depression in leads V_4 to V_6; 3 had S-T depression limited to leads V_1 to V_3. Twelve of the 30 patients were found to have no significant coronary artery disease; six of these had a positive treadmill test, with S-T depression limited to leads V_1 to V_3 in each.

Figures 1 and 2 show the resting and exercise electrocardiograms from two patients who had a positive treadmill test with S-T depression limited to leads V_1 to V_3. Coronary angiograms were normal in Patient 1 but revealed double vessel disease in Patient 2. Figure 3 shows the resting and exercise electrocardiograms from a patient who had a positive treadmill exercise test with S-T depression in leads V_4 to V_6. This patient had triple vessel coronary artery disease.

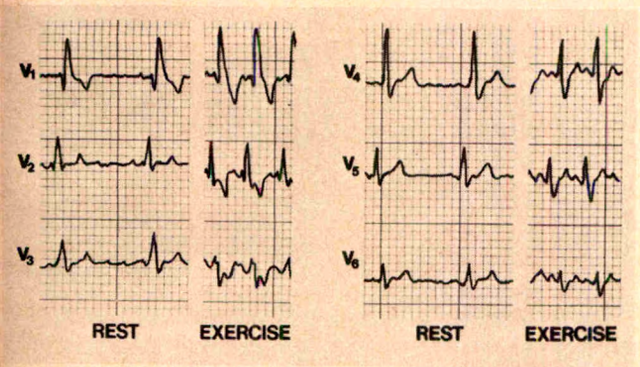


FIGURE 1. Leads V_1 to V_6 from the 12 lead electrocardiogram taken at rest with the patient standing and immediately after exercise in a patient with no significant coronary artery disease. S-T depression is noted in leads V_1 to V_3 in the postexercise tracing (redrawn from the original to enhance contrast). Time lines represent 0.1 second.

Discussion

Feil and Brofman[3] and Ellestad[4] have documented S-T segment depression in response to exercise in patients with right bundle branch block and arteriosclerotic cardiovascular disease. Lancaster et al.[5] reported no abnormalities of the S-T segment in the X-axis electrocardiographic lead on treadmill testing in 37 patients with right bundle branch block but without overt cardiac disease. Whinnery et al.,[1] using an X, Y, Z lead monitoring system, found no S-T segment depression in lead X or Y in 40 asymptomatic men with right bundle branch block. Eight of these men had significant coronary artery disease diagnosed with coronary angiography. The illustrations in their report did show exercise-induced S-T depression in the Z lead; however, the significance of this finding was not discussed. In a subsequent letter, Whinnery and Froelicher[6] explained that it was unclear whether the S-T segment vector moved in an anterior or posterior direction in response to exercise in normal men and indicated that the S-T depression in the Z lead at rest was similar to the pattern found in V_5 in left bundle branch block. They had previously reported[7] that S-T depression in lead V_5 in patients with left bundle branch block could not be used to make diagnostic decisions about these patients. Therefore, they suggested that additional S-T segment depression in the anterior precordial leads of patients with right bundle branch block may lack diagnostic significance. Our study confirms that S-T depression limited to the anterior precordial leads (V_1 to V_3) is not specific for coronary disease. When S-T depression was so limited, the false

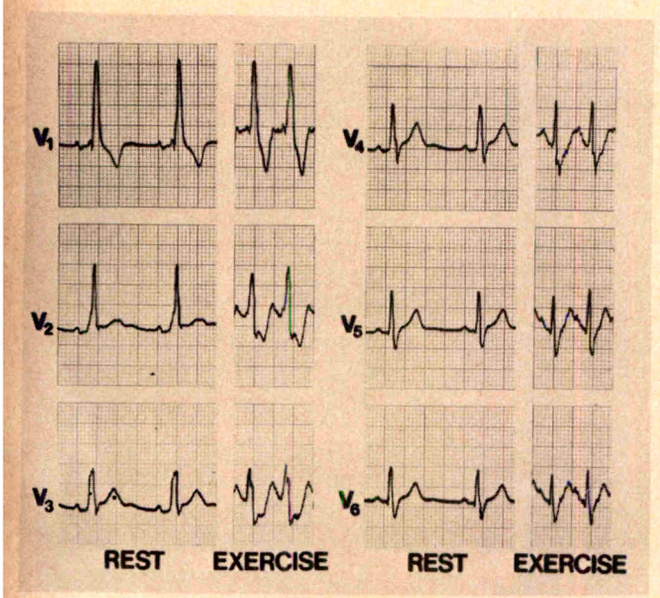


FIGURE 2. Leads V_1 to V_6 from the 12 lead electrocardiogram taken at rest with the patient standing and immediately after exercise in a patient with significant disease in the left anterior descending and circumflex coronary arteries. S-T depression is limited to leads V_1 to V_3 in the postexercise tracing. Time lines represent 0.04 second.

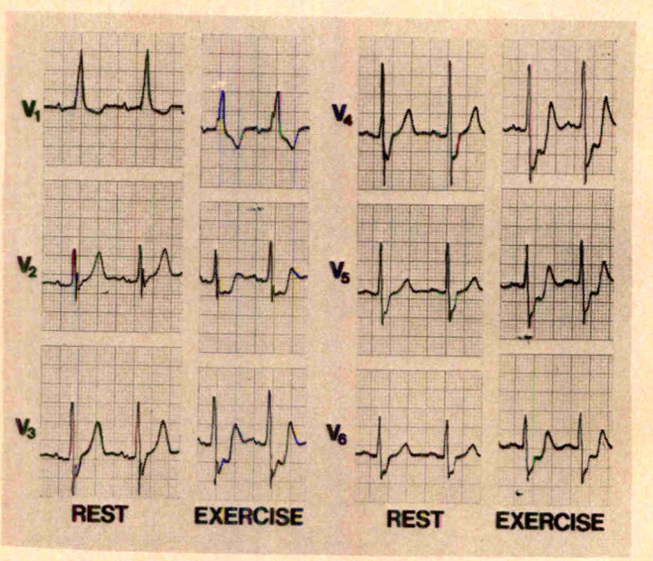


FIGURE 3. Leads V_1 to V_6 from the 12 lead electrocardiogram taken at rest with the patient standing and immediately after exercise in a patient with triple vessel coronary artery disease. S-T depression is noted in leads V_4 to V_6 as well as in V_1 to V_3 in the postexercise tracing. Time lines represent 0.04 second.

positive rate* of an abnormal test was 66 percent in patients with a diagnostic treadmill test.

S-T depression in leads V_4 to V_6 in right bundle branch block: Eight patients in our study had S-T depression in leads V_4 to V_6 during treadmill exercise testing, and all of these patients had significant multivessel coronary artery disease. This is in contrast to the result of Whinnery et al.,[1] who found no S-T depression during exercise in the X lead of eight patients with documented coronary artery disease. This discrepancy is best explained by the difference in the patient populations studied. Their patients were young asymptomatic air crewmen, and six of eight patients with coronary artery disease had only single vessel disease. It is well known that the submaximal treadmill exercise test is not sensitive in patients with these anatomic features.[8] Our patients were predominantly middle-aged, and all had symptoms suggestive of ischemic heart disease. All eight patients with S-T depression in leads V_4 to V_6 during exercise had multivessel coronary artery disease.

Clinical implications: In a patient population composed predominantly of men with symptoms of ischemic heart disease, we have found that the 12 lead submaximal treadmill exercise test has a sensitivity rate* of 69 percent and a specificity rate† of 45 percent in detecting coronary artery disease in the presence of right bundle branch block. The specificity of the treadmill test appears greater if S-T depression is recorded in leads V_4 to V_6. Therefore, the 12 lead submaximal exercise stress test can be useful in defining coronary artery disease in patients with right bundle branch block when S-T depression is noted in leads V_4 to V_6. S-T depression limited to leads V_1 to V_3 often represents a false positive exercise stress test.

* False positive rate of an abnormal test $= 100 - \frac{\text{true positive}}{\text{true positive} + \text{false positive}} \times 100.$

* Sensitivity $= \frac{\text{true positive}}{\text{true positive} + \text{false negative}} \times 100.$

† Specificity $= \frac{\text{true negative}}{\text{true negative} + \text{false positive}} \times 100.$

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Early Identification of Patients Developing Late In-Hospital Ventricular Fibrillation After Discharge From the Coronary Care Unit

A 5 1/2 Year Retrospective and Prospective Study of 1,897 Patients

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In an initial retrospective study, covering 3 years, 30 (3 percent) of 966 patients consecutively discharged from the coronary care unit, were found to have sustained late in-hospital ventricular fibrillation 10 to 38 days after myocardial infarction. Of these 30 patients, 18 (60 percent) died in the hospital and 14 (47 percent) had anteroseptal infarction complicated by right or left bundle branch block. In a later prospective study, covering 2 1/2 years, 47 consecutive coronary care unit survivors with anteroseptal infarction complicated by right or left bundle branch block were kept in the monitoring area for 6 weeks after infarction. Seventeen of these 47 (36 percent) sustained late in-hospital ventricular fibrillation. Neither the type nor the duration of bundle branch block affected the incidence of late in-hospital ventricular fibrillation. Six (35 percent) of the 17 patients with ventricular fibrillation died in the hospital. Three died from ventricular fibrillation, and of six patients treated with infarctectomy, another three died postoperatively. Of 11 hospital survivors with late in-hospital ventricular fibrillation, followed up for 1 to 30 months, 1 died suddenly within 1 month. Of the remaining 884 patients who were not kept in the monitoring area after coronary care unit discharge, 8 (0.9 percent) sustained late ventricular fibrillation (with 3 in-hospital deaths) and 4 (0.5 percent) others died suddenly in hospital. The results indicate that coronary care unit survivors with anteroseptal infarction complicated by right or left bundle branch block should be kept in the monitoring area for 6 weeks.

Late in-hospital ventricular fibrillation complicating acute myocardial infarction was initially considered to occur in patients with continuing cardiac failure[1] and to be associated with a poor immediate prognosis.[2] However, several reports[3–6] on cases of late ventricular fibrillation have indicated that 36 to 57 percent of patients survived to leave the hospital and 41 percent of the hospital survivors could be expected to survive for 5 years.[6] Although prolonged monitoring would probably reduce the hospital mortality of patients with late ventricular fibrillation,[7,8] indiscriminate prolonged monitoring would be impractical.[4,5] The purpose of this study was therefore to determine if one could identify a high risk group of patients for whom prolonged monitoring would be both practical and justified in terms of effectiveness.

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Methods

Retrospective study: The retrospective study was carried out from 1972 to 1974 in a consecutive series of patients who left the coronary care unit 3 to 7 days after the onset of acute myocardial infarction and who were expected to leave the hospital alive. Late in-hospital ventricular fibrillation was defined as ventricular fibrillation occurring in the after care department after the first week of infarction. Patients were included only if cardiac arrest was documented by

the presence of ventricular fibrillation. Excluded were patients with ventricular fibrillation secondary to shock, pulmonary edema, recurrent myocardial infarction, digitalis-intoxication or a pacemaker catheter. The diagnosis of acute myocardial infarction was based on a typical history of chest pain correlated with the appearance of diagnostic Q waves and evolutionary S-T segment or T wave changes and serial rise of serum enzymes (creatine kinase, glutamic oxaloacetic transaminase [SGOT] and lactic dehydrogenase). Infarction was localized according to criteria proposed by the New York Heart Association.[9] The size of infarction was estimated by measuring SGOT every 6 hours until the peak value was reached.

The stay in the coronary care unit ranged from 3 to 7 days, and during this period continuous electrocardiographic monitoring was performed in all patients, and a 14 lead electrocardiogram was obtained twice daily. Special attention was directed to possible early indications of late in-hospital ventricular fibrillation. These included the occurrence of major ventricular arrhythmias, supraventricular tachycardias, persistent sinus tachycardia, atrioventricular (A-V) nodal conduction disturbances, bundle branch block, a pericardial friction rub or heart failure. Patients with supraventricular tachycardias or conduction disturbances on admission were included in the study only if the rhythm or conduction disturbance was either transient or not evident in an electrocardiogram taken 6 months or less before admission. Persistent sinus tachycardia was defined as a sinus rate of more than 100 beats/min that developed after admission and persisted until the third day of infarction. Because antiarrhythmic intervention may influence the incidence of major ventricular arrhythmias,[10] these arrhythmias were studied only in patients whose antiarrhythmic therapy was withheld on purpose. During the latter study[11] continuous tape recording was performed during the first 12 hours of admission.

The presence and degree of heart failure were classified according to criteria proposed by Killip and Kimball.[12]

Prospective study: The prospective study was performed in all patients with acute myocardial infarction admitted to the coronary care unit from January 1975 to May 1977. During this study a subgroup considered to have a very high risk for development of late in-hospital ventricular fibrillation was kept in the monitoring area after coronary care unit discharge. The criteria for identification of this high risk group and the duration of prolonged monitoring were based on the results obtained from the retrospective study. The incidence and mortality of late in-hospital ventricular fibrillation were compared in the subgroup who underwent prolonged monitoring and in those who were not monitored after coronary care unit discharge. In addition, in the latter patients the incidence of late in-hospital sudden death was also determined.

The significance of differences between mean ages and mean peak values for SGOT were tested with Student's t test. A chi square test was used to test the significance of differences in incidence.

Results

Retrospective Study

During this 3 year study period 30 of 966 patients (3 percent) sustained late in-hospital ventricular fibrillation after discharge from the coronary care unit 10 to 38 days after the myocardial infarction. Late ventricular fibrillation occurred in seven patients during the second week after infarction, in nine during the third week, in seven during the fourth week, in six during the fifth week and in one during the sixth week. Immediately before late ventricular fibrillation 16 had no heart fail-

TABLE I

Characteristics of Patients With and Without Late In-Hospital Ventricular Fibrillation Admitted to the Coronary Care Unit During the Retrospective Study

	Late Ventricular Fibrillation (no. = 30)	Control Subjects (no. = 936)	*P* Value
Mean age (yr)	63.5	63.8	NS
Sex			
Male	26	673	NS
Female	4	263	
Previous infarction (%)	20	23	NS
Site of infarction			
Anterior	3 (10)	251 (27)	
Inferior	6 (20)	448 (48)	
Anterior and inferior	1 (3)	32 (3.3)	
Anteroseptal			
With BBB	14 (47)	26 (2.7)	<0.001
Without BBB	6 (20)	179 (19)	
Mean peak SGOT (IU)	192	104	<0.001
Complications			
Heart failure	25 (83)	204 (22)	<0.001
Supraventricular tachycardia	7	96	<0.05
Persistent sinus tachycardia	10	116	<0.005
Pericarditis	11	130	<0.005
A-V nodal block	2	70	NS
Ventricular tachycardia or fibrillation	2/11*	23/240*	NS
Hospital mortality (%) after CCU discharge	60	4 1/2	<0.001

* Patients whose antiarrhythmic therapy was withheld during the acute phase of myocardial infarction.
Figures in parentheses indicate percent. BBB = bundle branch block; CCU = coronary care unit; NS = not significant; *P* = probability; SGOT = serum glutamic oxaloacetic transaminase.

TABLE II

Duration and Type of Bundle Branch Block in Relation to Incidence of Late In-Hospital Ventricular Fibrillation in 40 CCU Survivors With Anteroseptal Infarction and Bundle Branch Block Admitted During the Retrospective Study

Bundle Branch Block	Patients (no.) Total	With Late Ventricular Fibrillation
Transient	28	9
Persistent	12	5
Left bundle branch block	3	1
Right bundle branch block	18	6
Right bundle branch block with concomitant hemiblock	19	7

CCU = coronary care unit.

ure and 14 had moderate heart failure (Killip class II).

Factors related to late in-hospital ventricular fibrillation: Patients with and without late ventricular fibrillation were comparable with respect to age, sex, number of previous infarctions and incidence of A-V nodal block (Table I). Factors shown to be significantly related to the development of late in-hospital ventricular fibrillation were anteroseptal infarction complicated by bundle branch block, peak SGOT level, presence of heart failure in the coronary care unit, persistent sinus tachycardia, supraventricular tachycardia and pericarditis (Table I). Fourteen of 40 patients (35 percent) in the subgroup with anteroseptal infarction complicated by bundle branch block sustained late in-hospital ventricular fibrillation. Neither the duration or type of bundle branch block nor the presence of concomitant hemiblock affected the incidence of late in-hospital ventricular fibrillation (Table II). Although 83 percent of patients with late in-hospital ventricular fibrillation had heart failure in the coronary care unit, the incidence of late in-hospital ventricular fibrillation in the 229 patients with heart failure was 11 percent compared with 35 percent in the 40 patients with bundle branch block and anteroseptal infarction (Table III).

Recurrent ventricular fibrillation: Twenty patients had recurrent attacks of ventricular fibrillation. In 16 of these, ventricular fibrillation was initiated by rapid ventricular tachycardia (170 to 220 beats/min). Fifteen patients had recurrences that were refractory to antiarrhythmic intervention, cardiac pacing and repeated defibrillation. Two of these 15 were successfully treated by infarctectomy, and the other 13 died. In the other 15 patients who were initially responsive to treatment, 5 subsequently died, presumably because of a delay in instituting cardiopulmonary resuscitation. At postmortem examination a ventricular aneurysm was found in all 18 deaths.

Follow-up: Of the 12 hospital survivors with late ventricular fibrillation, 2 died within 1 year from sudden death and a recurrent infarction, respectively. The remaining 10 patients followed up from 30 to 40 months are still alive. Five of these 10 patients are still receiving antiarrhythmic therapy (quinidine or procainamide).

TABLE III

Incidence of Late In-Hospital Ventricular Fibrillation in CCU Survivors With Bundle Branch Block Complicating Anteroseptal Infarction and in Those With Heart Failure in the CCU (Retrospective Study)

	Anteroseptal With Bundle Branch Block (no. = 40)	Heart Failure in CCU (no. = 229)
Mean age (yr)	63.3 ± 9.2	65.7 ± 9.7
Sex		
Male	31	161
Female	9	68
Mean peak SGOT (IU)	192	209
Previous infarction (%)	18	21
Supraventricular tachycardia (%)	25	28
Sinus tachycardia (%)	30	31
Pericarditis (%)	28	29
Late ventricular fibrillation (%)	35	11

CCU = coronary care unit; SGOT = serum glutamic oxaloacetic transaminase.

Prospective Study

Of the 30 patients who sustained late in-hospital ventricular fibrillation, 14 (47 percent) had anteroseptal infarction complicated by right or left bundle branch block. Consequently during the 2 1/2 year prospective study, 47 of 931 coronary care unit survivors who had anteroseptal infarction complicated by bundle branch block were kept for 6 weeks in the monitoring area. Seventeen of these 47 (36 percent) sustained late in-hospital ventricular fibrillation. Fifteen had right bundle branch block and 2 left bundle branch block. Of the 884 coronary care unit survivors who were not kept in the monitoring area, 3 died suddenly in hospital and 8 sustained late in-hospital ventricular fibrillation.

The coronary care unit data of all these 28 patients with either late in-hospital ventricular fibrillation or late in-hospital sudden death were not different from those of the retrospective study. Late in-hospital ventricular fibrillation or sudden death occurred in 8 patients during the second week after infarction, in 10 during the third week, in 6 during the fourth week, in 3 during the fifth week and in 1 during the sixth week.

Initiation of ventricular fibrillation: During prolonged monitoring of the 17 patients with late in-hospital ventricular fibrillation, 5 showed runs of ventricular ectopic beats 12 hours to 3 days before the onset of ventricular fibrillation. The ventricular fibrillation in 14 of these 17 patients was initiated with a ventricular tachycardia (ventricular rate 180 to 220 beats/min) that deteriorated into ventricular fibrillation.

Treatment: Although all 17 patients underwent successful defibrillation, 9 had recurrences that were unresponsive to intravenous antiarrhythmic treatment, cardiac pacing and repeated defibrillation. Six of these nine patients underwent left heart catheterization, which revealed a large ventricular aneurysm in all and a low ejection fraction ranging from 0.35 to 0.50. In all

six an infarctectomy was performed 2 to 6 weeks after infarction. Three of these six patients were successfully treated, but the other three died during the postoperative course. The three other patients with recurrences died before an emergency infarctectomy could be performed.

Follow-up: All 11 hospital survivors with late in-hospital ventricular fibrillation who were in the monitoring area for 6 weeks after infarction were discharged with antiarrhythmic therapy (quinidine or procainamide). However, 1 of these 11 died suddenly 2 weeks after discharge. The remaining 10 patients are still alive after a follow-up period of 1 to 30 months.

Discussion

Identification of patients at high risk for late in-hospital ventricular fibrillation: Previous studies of patients with late in-hospital ventricular fibrillation or sudden death[5,6,8,13] have drawn attention to the more frequent occurrence in these patients of factors such as an anterior site of infarction, large size of infarction, the presence of heart failure, history of certain major arrhythmias in the coronary care unit and persistent S-T segment elevation. However, these factors are not specific enough to identify a group of patients in whom long-term monitoring is likely to be both feasible and necessary. In our retrospective and prospective studies we identified patients with anteroseptal infarction complicated by bundle branch block as having an incidence rate of late ventricular fibrillation of 35 and 36 percent, respectively, and these rates appear to justify the burdens posed by long-term monitoring. Because this subgroup accounts for only 5 percent of all coronary care unit survivors of acute myocardial infarction, continuous monitoring of these patients even for 6 weeks should not lead to administrative and financial problems. Although our prospective data suggest that the immediate prognosis of these patients improved as a result of long-term monitoring through earlier initiation of cardiopulmonary resuscitation, prophylactic antiarrhythmic therapy in a subset of this high risk group might be another way of managing these patients. Such prophylactic therapy was not evaluated in our study but deserves further examination.

Pathologic significance of anteroseptal infarction with bundle branch block: The association between a typical type of infarction such as anteroseptal infarction complicated by bundle branch block and late in-hospital ventricular fibrillation was also apparent in previous reports.[14,15] In our study the hallmark of the high risk group with these findings was the presence of bundle branch block, however transient, in the setting of acute anteroseptal infarction. Consideration of the pathophysiologic significance of this block raises several possibilities. The first is related to the size and site of myocardial infarction. Bundle branch block typically signifies a proximal occlusion of the left anterior descending artery and therefore a massive anteroseptal infarction.[16] In our experience[17] anteroseptal infarction is usually associated with a large incidence of pump failure and has a poor prognosis. Therefore, patients with an anteroseptal infarct may be more susceptible to deterioration of mechanical function, which in turn may initiate secondary arrhythmic mechanisms. The second possibility relates to our findings of ventricular aneurysm during cardiac catheterization or post-mortem examination; it might be that the mechanisms for arrhythmias in these patients are the same as those operative in chronic aneurysm. Finally, involvement of the bundle branches itself may predispose to the establishment of unstable reentrant circuits in the Purkinje system.

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Initiation of Repetitive Ventricular Depolarizations By Relatively Late Premature Complexes in Patients With Acute Myocardial Infarction

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To determine whether repetitive ventricular depolarizations are more commonly precipitated by early compared with late premature ventricular complexes, we analyzed continuous electrocardiographic recordings obtained during the first 10 hours in 38 patients with myocardial infarction without shock with the Argus/H computer system with editor verification of all premature ventricular complexes. Episodes of repetitive ventricular depolarization were defined as two or more consecutive complexes at a rate of 120 beats/min or greater. Premature ventricular complexes occurring with coupling intervals from the preceding normal complex equal to or less than the Q-T interval of the normal complex were defined as early, and those with longer coupling intervals as late. Among all premature ventricular complexes, early premature ventricular complexes accounted for 38 percent. The average coupling interval of premature ventricular complexes from a preceding normal complex did not correlate with heart rate, blood pressure, infarct size estimated enzymatically, the electrocardiographic locus of infarction or history of previous infarction. Twenty-nine patients had a total of 337 episodes of repetitive ventricular depolarizations. Somewhat surprisingly, 78 percent of these episodes, and all episodes in 22 patients, were initiated by late premature ventricular complexes. Thus, repetitive ventricular depolarizations in patients with acute myocardial infarction are often precipitated by late rather than early premature ventricular complexes.

Continuous electrocardiographic monitoring of patients in coronary care units has established the importance of premature ventricular complexes in the initiation of ventricular tachycardia and ventricular fibrillation. Early premature ventricular complexes have appeared to be particularly malignant,[1–6] apparently because they occur at a time when repolarization is incomplete and the ventricle is therefore particularly vulnerable to malignant arrhythmia.[1,2] It is clear that in experimental animals subjected to myocardial ischemia, repetitive ventricle depolarizations can be induced readily by stimulation of the heart during the vulnerable period. The most widely accepted clinical criteria characterizing hazardous premature ventricular complexes in patients include electrocardiographic proximity of the premature complex to the T wave of the preceding beat.[3,7] On the other hand, under some circumstances ventricular tachycardia may be initiated by late premature ventricular complexes, and perhaps even more striking, ventricular fibrillation may occur without any warning arrhythmia and without a discrete initiating premature ventricular complex. These distinctions may be far from trivial, for they may reflect fundamentally different electrophysiologic mechanisms responsible for sudden death in ambulatory patients with ischemic heart disease as well as for malignant arrhythmia in patients hospitalized with acute myocardial infarction.

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This study was performed to characterize the relative frequency with which early compared with late premature ventricular complexes initiate repetitive ventricular depolarizations in patients hospitalized with acute myocardial infarction. Accordingly, continuous electrocardiographic recordings from 38 patients with acute myocardial infarction during the first 10 hours after admission to the coronary care unit were analyzed by computer to quantify ventricular arrhythmia. The frequency of premature ventricular complexes and coupling intervals from normal supraventricular beats to each premature ventricular complex preceded by a normal complex were analyzed in relation to the incidence, severity and initiation of repetitive ventricular depolarizations. Results were assessed also in relation to blood pressure, heart rate, site of infarction, history of previous infarction and enzymatically estimated infarct size based on analysis of serial changes in plasma creatine kinase (CK) activity.

Methods

Patients studied: Thirty-eight patients with acute myocardial infarction were selected for study. They were selected on the basis of the following criteria: (1) admission to the coronary care unit within 4 hours of the onset of symptoms, and (2) the presence of at least 10 premature ventricular complexes during the 10 hour recording interval. None exhibited profound hemodynamic decompensation (blood pressure 95/70 mm Hg or greater, heart rate 140 beats/min or less, urinary output 20 ml/hour or greater and arterial partial pressure of oxygen 60 mm Hg or greater). In each case, myocardial infarction was documented by serial electrocardiographic changes, elevated plasma enzymes including the MB isoenzyme of CK and positive technetium-99m pyrophosphate scintigrams. The group comprised 22 men and 16 women with a mean age of 58 years (range 36 to 81). Fifteen patients had had a previous remote myocardial infarction (documented electrocardiographically and on the basis of plasma enzyme changes more than 3 months before the new episode), and the remainder had no apparent previous infarction. The site of infarction was judged anterior in 22 patients, inferior in 14 and lateral in 2, on the basis of electrocardiographic and scintigraphic criteria. All patients survived for at least 72 hours and were transferred from the coronary care unit within 5 days after admission.

TABLE I

Patients Categorized According to Infarct Size

	Infarct Size Index*		
	<25 (no. = 12)	25–50 (no. = 13)	>50 (no. = 13)
Heart rate (beats/min)†	88 ± 9	83 ± 6	85 ± 11
Infarct size index†	14 ± 2	31 ± 2.4	58 ± 4.6
Total number of PVCs†	123 ± 41	186 ± 80	279 ± 62
Lidocaine dose (mg)‡	590 ± 82	675 ± 79	710 ± 94
Patients with previous myocardial infarction (no.)	6	4	5

* In CK-gram-equivalents/m^2 body surface area.
† Expressed as mean ± standard error of the mean.
‡ Cumulative amount administered during the 10 hour recording interval.
PVCs = premature ventricular complexes.

Protocol: Continuous 10 hour electrocardiographic recordings were initiated within 2 hours of admission of each patient to the unit. Patients with 10 or more premature ventricular complexes per minute or two or more consecutive premature ventricular complexes were treated with bolus injections of lidocaine (1 mg/kg intravenously). If severe arrhythmia persisted, defined by the same criteria after two bolus injections within 20 minutes of each other, lidocaine was administered by continuous infusion and a diary was kept to record the total amount of lidocaine given. The mean total amount of lidocaine administered to patients in each group classified on the basis of infarct size is shown in Table I.

Serial blood samples for analysis of plasma CK and MB CK[8] were obtained hourly through an indwelling heparin lock for the first 10 hours and at 4 hour intervals for a total of 72 hours. The extent of infarction was estimated enzymatically based on cumulated CK released into plasma.[9] To avoid potential

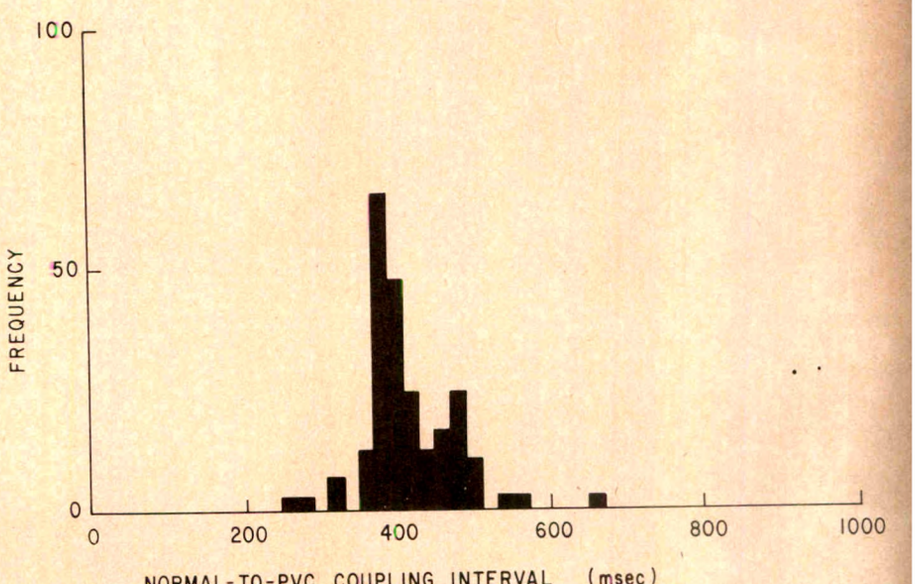


FIGURE 1. Histogram of coupling intervals from one patient during the 10 hour recording interval. Coupling intervals are measured from the onset of a preceding normal complex to the onset of an isolated premature ventricular complex (PVC) or of the initial premature ventricular complex of a repetitive arrhythmia.

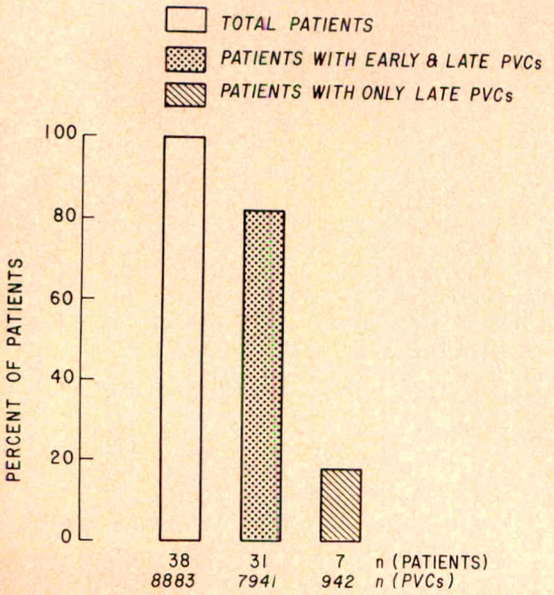


FIGURE 2. The distribution of patients with early and late premature ventricular complexes (PVCs). The **center bar** shows the percent of patients who exhibited both early (3,256) and late (4,685) premature ventricular complexes. The **bar on the right** shows the percent of patients who exhibited only late premature ventricular complexes. None had only early premature complexes. n = number.

influences of cardiac catheterization on ventricular arrhythmia, hemodynamic changes were not monitored invasively until the completion of the 10 hour recording interval.

Analysis of electrocardiographic recordings: Continuous electrocardiographic recordings on magnetic tape were analyzed with the use of the Argus/H computer system, permitting automated detection and quantification of premature ventricular complexes at 60 times real time with human editor verification of all abnormal electrocardiographic complexes.[10] Analysis incorporated three steps including (1) digitization of the electrocardiographic recording at a sampling frequency of 250/sec, (2) automated detection and quantification of premature ventricular complexes by the computer system based on analysis of the digitized signal as previously described,[11] and (3) definitive assignment of all potentially abnormal complexes detected by the computer to the appropriate category (supraventricular, ventricular or borderline).[12] The Argus/H computer system provides a sensitivity rate for detection of premature ventricular complexes of approximately 90 percent, reproducibility rate after digitization of ±0.1 percent and essentially no false positive results.[10] Data from automated analysis include the following: the frequency distribution of premature ventricular complexes, heart rate, couplets and runs of three or more premature ventricular complexes; coupling intervals from the preceding normal beat to each premature ventricular complex initiating repetitive depolarizations; and coupling intervals of all isolated premature ventricular complexes measured from the onset of the preceding normal beat to the onset of the premature ventricular complex. An example of the output describing coupling intervals is shown in Figure 1.

Repetitive ventricular depolarizations were defined as two or more premature ventricular complexes occurring consecutively at a rate of 120/min or greater. Early premature ventricular complexes were defined as those with coupling intervals equal to or less than the Q-T interval of the preceding normal complex. Late premature ventricular complexes were defined as those with coupling intervals greater than the Q-T interval of the preceding normal complex.

Results

Heart rate averaged 79 beats/min (range 54 to 118) during the 10 hour recording interval. All patients exhibited premature ventricular complexes; the average frequency during the 10 hour interval was 234 ± 54 (mean ± standard error of the mean) (Fig. 2). Thirty-one patients (82 percent) exhibited both early and late premature ventricular complexes (total 7,941 complexes, of which 3,256 [41 percent] were early). The remaining seven patients (18 percent) exhibited only late premature ventricular complexes (total 942 complexes or 11 percent of all abnormal complexes). No patient exhibited only early premature ventricular complexes. Thus, 38 percent of all isolated premature ventricular complexes plus premature ventricular complexes initiating couplets or runs occurred early.

Early versus late premature ventricular complexes: Relation to repetitive ventricular depolarizations: Twenty-nine patients (76 percent) manifested repetitive ventricular depolarizations (total 337 episodes) (Fig. 3). Seventy-eight percent of these episodes were initiated by a late premature ventricular complex. Because 38 percent of all isolated premature ventricular complexes were early, the initiation of repetitive ventricular depolarizations by late premature ventricular complexes was significant at the $P < 0.01$ level. Only 22 percent (52 episodes) of repetitive ventricular depolarizations were initiated by early premature ventricular complexes.

Repetitive ventricular depolarizations were categorized as couplets (two consecutive premature ventricular complexes) or runs of ventricular tachycardia (three or more consecutive premature ventricular complexes). Twenty-nine patients exhibited at least one couplet or run during the 10 hour recording interval. Among the total of 245 couplets, 84 percent were initiated by a late premature ventricular complex (Fig. 4). Similarly, among the 92 episodes of runs of ventricular tachycardia, 86 percent were initiated by a late premature ventricular complex. Only two episodes of ventricular fibrillation occurred during the recording interval; both were initiated by late premature ventricular complexes.

Relation to coupling interval: Although the prevalence of repetitive ventricular depolarizations correlated with the frequency of isolated premature ventricular complexes (Table I) ($r = 0.8$), it was not related to the average coupling interval expressed in absolute terms or as a fraction of the average Q-T interval of normal beats. In addition, the coupling interval of isolated premature ventricular complexes or of premature ventricular complexes initiating couplets or runs failed to correlate with the number of complexes and runs exhibited by the same patient, enzymatically estimated infarct size, heart rate, the site of infarction or the presence or absence of previous infarction.

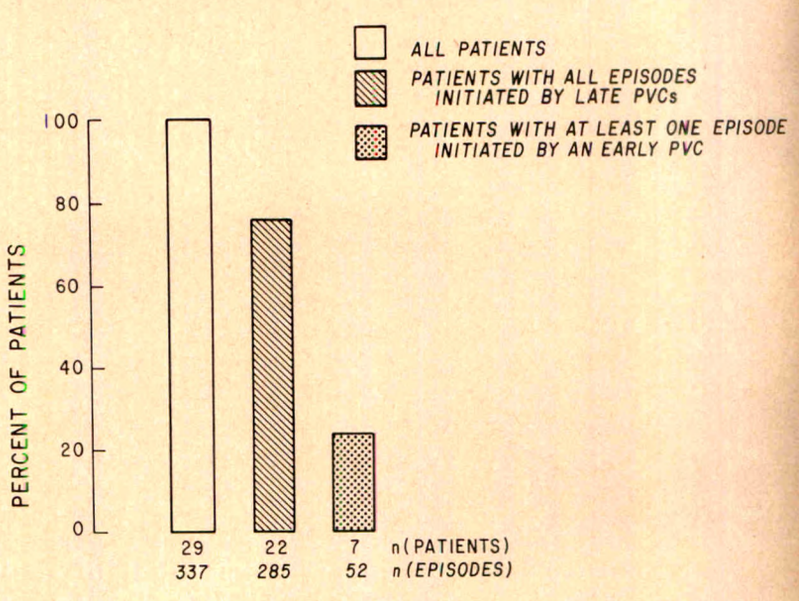


FIGURE 3. Initiation of repetitive depolarizations by early and late premature ventricular complexes (PVCs). Twenty-nine patients had 337 episodes of repetitive ventricular depolarizations, of which 285 were initiated by late premature ventricular complexes. n = number.

Discussion

Ventricular premature complexes are the most common manifestation of electrophysiologic derangements accompanying myocardial infarction.[4–6,13] Their occurrence during the vulnerable period of the cardiac cycle, during which electrical stimulation is prone to result in ventricular tachycardia or fibrillation, is viewed with particular alarm on the basis of many experimental and clinical observations. For example, after ligation of the left coronary artery in dogs, exogenous electrical stimulation with low energy produces ventricular tachycardia that frequently deteriorates into ventricular fibrillation. In addition, ventricular fibrillation after occlusion of the circumflex branch of the left coronary artery in anesthetized dogs is frequently associated with premature ventricular complexes occurring in close proximity to the apex of the T wave.

Significance of late ventricular premature complexes: One certainly cannot deny that exogenous or endogenous electrical stimulation of the ischemic heart during a patient's vulnerable period can give rise to analogous phenomena. On the other hand, the relative importance of late premature ventricular complexes (those that occur after the inscription of the T wave) may have been underestimated. For example, among 52 patients with acute myocardial infarction, de Soyza et al.[14] observed that the mean coupling interval of isolated premature ventricular complexes in patients with ventricular tachycardia was virtually identical to that in patients without this complication. Bleifer et al.[15] found no association between the "R on T phenomenon" and ventricular tachycardia in 21 ambulatory patients unless couplets or frequent premature ventricular complexes (12/min or more) were present concomitantly; and Williams[16] and Scherlag[17] and their co-workers noted initiation of ventricular fibrillation by late premature ventricular complexes in 7 of 17 patients with acute myocardial infarction and the absence of ventricular fibrillation despite the presence of the "R

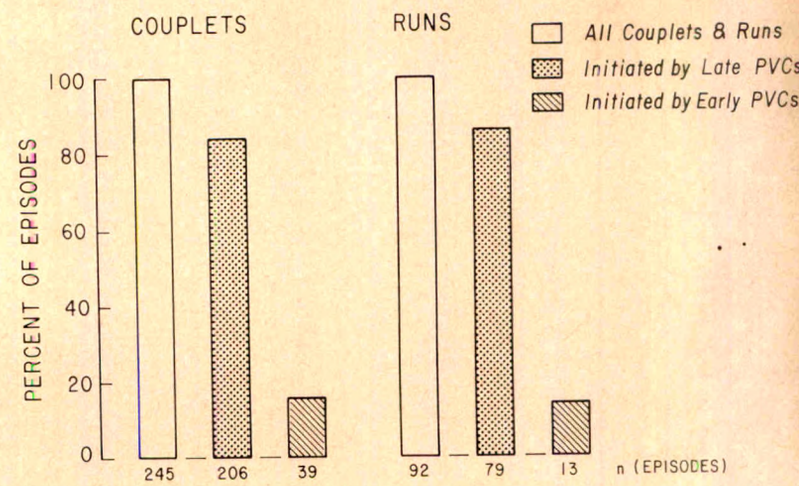


FIGURE 4. Initiation of both couplets and runs of ventricular complexes by early and late premature ventricular complexes (PVCs). Episodes of couplets (two consecutive premature ventricular complexes) are shown on the **left,** and runs (three or more consecutive premature ventricular complexes) on the **right.** Late premature ventricular complexes initiated 206 of 245 couplets and 79 of 92 runs. n = number.

on T phenomenon" in 49 percent of patients studied. Even in the canine model, spontaneous ventricular tachycardia has been associated with long coupling intervals and initiation of repetitive depolarizations by late premature ventricular complexes.[16]

In this study, 84 percent of all couplets, 86 percent of all episodes of ventricular tachycardia and the two episodes of ventricular fibrillation were initiated by late premature ventricular complexes. The possibility that treatment with lidocaine may have contributed to the apparent propensity of late premature ventricular complexes to initiate these repetitive ventricular depolarizations must be considered because the drug may have selectively affected one class of premature ventricular complexes or its sequelae. Lown and Vassaux,[18] Mogensen[19] and others demonstrated that lidocaine diminishes repetitive ventricular depolarizations. However, in our study the amount of lidocaine administered and the temporal relation between its administration and the occurrence of repetitive ventricular depolarizations were similar in patients with repetitive depolarizations initiated by early and late premature ventricular complexes. Among patients categorized in three groups according to enzymatically estimated infarct size, the cumulative lidocaine dose did not vary markedly, although a somewhat smaller dose was required in patients with the smallest infarcts.

Electrophysiologic mechanisms: Our observations indicate that premature ventricular complexes occurring with relatively long coupling intervals in patients hospitalized with acute myocardial infarction frequently initiate repetitive ventricular depolarizations. It appears likely that several different electrophysiologic mechanisms may contribute to ventricular arrhythmia in patients with acute myocardial infarction.[17,20,21] In our study the majority of both early and late premature ventricular complexes exhibited considerable variation in the coupling intervals (Fig. 1). Schamroth[22] suggested that early premature complexes with rigidly fixed coupling intervals may reflect reentry. Premature ventricular complexes with no fixed coupling interval are more compatible with parasystole, and late diastolic extrasystoles with ventricular tachycardia due to increased automaticity with high degrees of exit block. According to these interpretations, the ventricular arrhythmia occurring in our patients was probably due to automaticity rather than reentry. Early after the onset of ischemic injury, reentry within the myocardium appears to be a prominent factor. Somewhat later, enhanced automaticity may be more important. Later, in patients convalescing from myocardial infarction, malignant ventricular arryhthmia may be due to enhanced automaticity of surviving Purkinje fibers near the region of previous infarction.

Implications: It is not clear whether the electrophysiologic mechanisms underlying the relatively late premature ventricular complexes seen in our study in patients hospitalized with acute myocardial infarction differ from those giving rise to early premature ventricular complexes at the same time in the same patients. It is also not yet clear whether disparate fundamental mechanisms such as fast primary inward current in contrast to slow secondary inward current give rise to repetitive ventricular depolarizations and, if so, whether each is associated with a particular class of premature complexes. We cannot exclude the possibility that in some patients early or late premature ventricular complexes, or both, may be manifestations of an underlying electrophysiologic instability of the heart that gives rise to repetitive ventricular depolarization independently. However, the frequent initiation of repetitive ventricular depolarizations by late premature ventricular complexes attests to their potential importance as warning arrhythmias on the one hand, and as precipitants of malignant arrhythmias that may require pharmacologic suppression on the other.

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Time-Related Changes in the Q-T Interval in Acute Myocardial Infarction: Possible Relation To Local Hypocalcemia

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In 63 patients with either acute transmural or nontransmural myocardial infarction, the Q-T interval was prolonged beyond normal limits on at least 1 of the 5 days after infarction in 27 patients (8 with transmural and 19 with nontransmural infarction). The time-related changes in the corrected Q-T (Q-Tc) interval were defined for the entire sample and showed significant expansion, maximal on day 2, from a preinfarction control value. By day 5, the Q-Tc interval was no longer significantly prolonged and was not expanded beyond normal limits in any patient. Various possible causes of Q-T prolongation in myocardial infarction are local hypothermia, local conduction delay, neurogenic effect and local hypocalcemia. Collateral evidence suggests that the latter may contribute significantly to prolongation.

The Q-T interval of the electrocardiogram represents the time required for ventricular depolarization and repolarization. One of its two components, the QRS interval, is independent of heart rate. Rate-proportional shortening of the ventricular muscle action potentials is the reason for contraction of the ST-T component. Q-T prolongation occurs when there is a delayed or expanded repolarization phase, uniform or regional, in the ventricular myocardium. It may occur in association with use of quinidine-like drugs,[1] neurogenic mechanisms,[2] congenital syndromes,[3,4] hypothermia[5] and electrolyte disturbances such as hypocalcemia, as well as in myocardial diseases such as mitral valve prolapse,[6] myocarditis[7] and myocardial infarction.[8–10]

In this study, quantitative measurements of the Q-T duration were made daily for 2 weeks in patients with acute myocardial infarction to determine time-related changes in this interval.

Material and Methods

Selection of patients: Patients admitted to the hospital between July 1974 and July 1976 with a final diagnosis of acute myocardial infarction were studied retrospectively. The diagnosis of definite myocardial infarction in this study required all three of the following criteria: (1) Onset of ischemic pain, acute dyspnea or syncope within the 48 hours preceding admission. Two patients who sustained a perioperative myocardial infarction were also included (these criteria were designed to ensure that admission to the study was due to onset, rather than extension, of an infarct). (2) Appropriate electrocardiographic changes suggesting either acute transmural infarction (pathologic Q waves, S-T elevation with evolution) or nontransmural infarction (evolving T wave inversions). (3) Diagnostic elevation of serial enzyme activity, the highest value exceeding the normal range and at least 100 percent greater than the lowest value.

Patients were excluded for any of the following reasons: (1) serum calcium greater than 11.3 or less than 8.2 mEq/liter; (2) serum potassium greater than 5.8 or less than 3.4 mEq/liter; (3) use of quinidine, procainamide or phenothiazines; (4) pericarditis; or (5) cerebrovascular accidents.

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Collection of data: All electrocardiograms taken during the 14 days after infarction were reviewed. When available, electrocardiograms taken before infarction were also examined. Daily electrocardiograms for the first 6 days after infarction were available for 92 percent of patients. When more than one tracing was available for a given day, the first one was used.

All measurements of the Q-T interval were made by the same investigator (R.D.) in all 12 leads according to the method of Lepeschkin and Surawicz.[11] Care was taken to avoid measurement of an "overshoot." The longest Q-T interval of the electrocardiogram was used in computation; more than 7,900 Q-T intervals were measured. In the eight patients with an intraventricular conduction defect (defined as a QRS interval greater than 0.10 second), the adjusted Q-T interval duration, obtained by subtracting 0.08 second from the observed QRS duration and subtracting this difference from the total Q-T interval,[12] was used in computation. The Q-T limits of normal for various heart rates are listed in Table I. These values were assembled by the late Hans Hecht from data compiled in Frank Wilson's laboratory. These unpublished tables have been used for the last 29 and 13 years, respectively, at the Universities of Utah and Chicago. The formula Q-Tc = Q-T/R-R was used to correct the Q-T interval for heart rate.[13]

The depth of T wave inversion was measured from the base of the line at the isoelectric P-R segment to the base of the line at the apex of the T wave. The deepest T wave inversion of the electrocardiogram was used in computation.

Statistical analysis: The significance of differences between mean values was calculated using Student's *t* test. Categorical data were analyzed with the chi-square method. *P* values of less than 0.05 were considered significant.

Results

Incidence of Q-T prolongation: Seventy-one patients were included in the study. Eight patients had an intraventricular conduction defect; none of them had abnormal Q-T prolongation during infarction. Fourteen

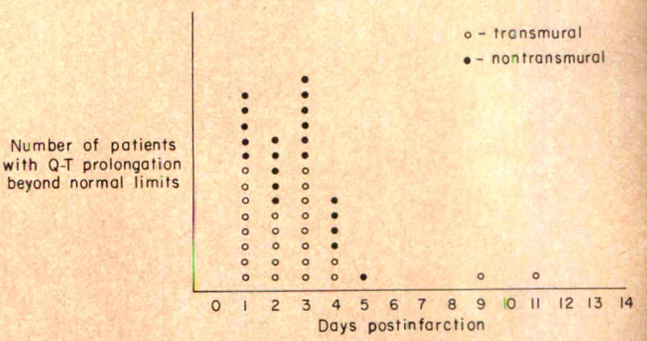


FIGURE 1. Number of patients with prolongation of the Q-T interval beyond normal limits (see Table I).

of the remaining 63 patients (22 percent) had acute nontransmural myocardial infarction, and 49 (78 percent) had acute transmural myocardial infarction.

In at least one tracing during the first 5 days after infarction, lengthening of the Q-T interval beyond normal limits was found in 27 of the 63 patients (43 percent) and was more common in patients with nontransmural (8 of 14, 57 percent) than in those with transmural (19 of 49, 39 percent) infarction. The difference was not significant. The distribution by day of Q-T prolongation is shown in Figure 1. By day 6, regardless of the magnitude of preceding Q-T prolongation, all intervals were again within normal limits.

One patient exhibited Q-T prolongation beyond normal limits on day 9. He had a transmural infarction with a prolonged Q-T interval on days 3 and 4 and a normal interval on day 5. He continued to have pain throughout hospitalization but showed no clinical evidence of infarct extension. He had four vessel coronary bypass grafts 1 month later. One patient with transmural infarction had Q-T prolongation beyond

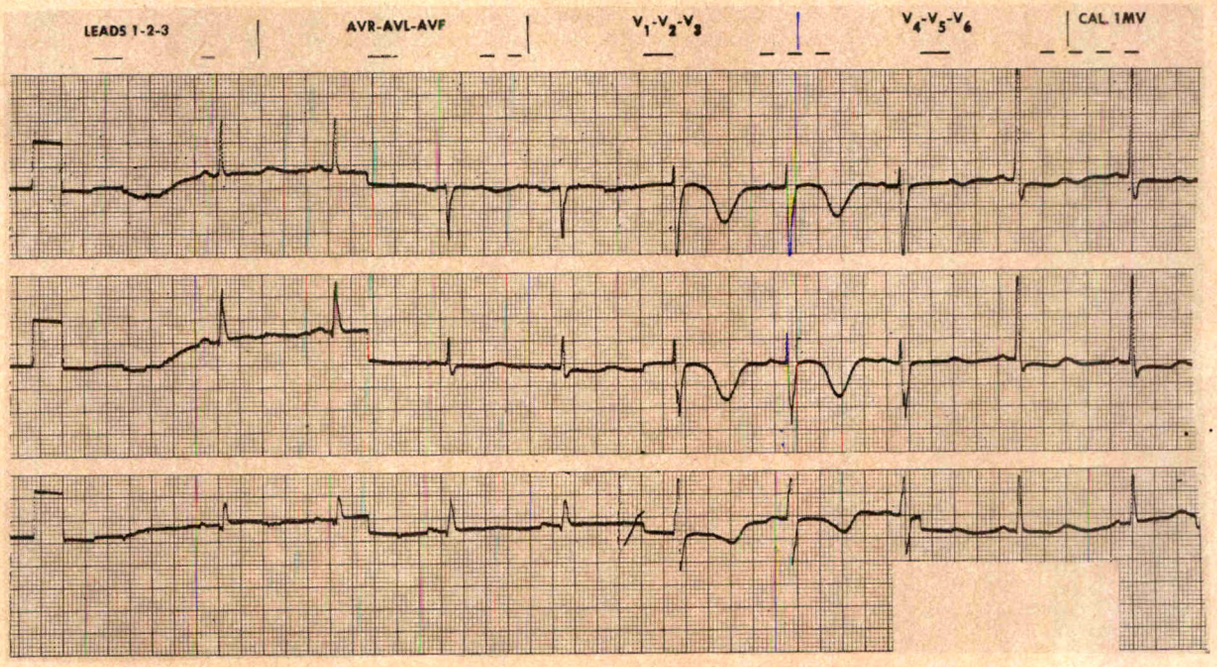


FIGURE 2. Electrocardiogram on day 3 of a patient with nontransmural infarction. The Q-T interval is 0.60 second. CAL. = calibration.

TABLE I

Q-T Interval: Normal Limits in Relation to Heart Rate

Heart Rate (beats/min)	Q-T Duration (sec)
45–50	0.40 to 0.51
51–55	0.38 to 0.50
56–60	0.36 to 0.48
61–65	0.35 to 0.45
66–70	0.34 to 0.43
71–75	0.33 to 0.42
76–80	0.32 to 0.41
81–85	0.31 to 0.39
86–90	0.29 to 0.38
91–95	0.29 to 0.37
96–100	0.29 to 0.36
101–105	0.28 to 0.35
106–110	0.29 to 0.35
111–115	0.29 to 0.35
116–120	0.27 to 0.32
120–150	0.25 to 0.30

normal limits on day 11. On day 13 he complained of chest pain; the electrocardiogram and enzyme changes suggested infarct extension.

Relation to infarct location: Abnormal Q-T prolongation within the first 5 days of infarction was not related to the site of the infarct. It occurred in 7 of 19 (37 percent) patients with inferior infarction and 12 of 30 (40 percent) with anterior infarction. Among patients with nontransmural infarction, an abnormal Q-T interval was more common in those with anterior (7 of 10, 70 percent) than in those with inferior (1 of 4, 25 percent) infarction, but the difference was not significant. The longest Q-Tc values were found in patients with nontransmural infarction (Fig. 2).

Comparison with patients' control or average Q-T interval: We considered it desirable not only to examine the deviations of the Q-T interval with respect to the normal limits of Table I, but also to compare on successive days the mean corrected Q-T value with the "average" value for this patient sample. *The mean preinfarction Q-Tc interval* was selected as the control value (day 0) for this purpose. It was obtained from those patients (43 percent) whose prior tracing was available to us. With these data we could examine the natural history of the Q-Tc interval expressed as a statistical trend for the entire patient sample.

Table II lists the day 0 control value for the Q-Tc interval in 7 of 14 patients (50 percent) with nontransmural infarction (group A), 20 of 49 patients (41 percent) with transmural infarction (group B) and 27 of 63 patients (43 percent) of groups A and B combined. By day 5, regardless of the magnitude of prolongation on earlier days, the mean Q-Tc interval was not signficantly prolonged in any group and did not again become significantly prolonged through day 14 after infarction. At all times the mean Q-Tc interval was greater in group A (nontransmural infarction) than in group B (transmural infarction), but the difference was not significant. By day 14, the mean Q-Tc interval had returned almost to control level in all groups. These data indicate that, although many patients had no prolongation of the Q-Tc interval beyond the outer limit of normal, the interval underwent a transient expansion during the first 5 days after acute myocardial infarction. The time course of changes in the mean Q-Tc interval was similar in all groups (Fig. 3). The mean Q-Tc prolongation was greatest in all groups on day 2, followed by days 3, 1, 4 and 5.

There was no correlation between the duration of the Q-Tc interval and the magnitude of the depth of T wave inversion in patients with either nontransmural or transmural infarction.

Association with serum enzyme values: There was no association between peak creatine kinase (CK) values and the presence of transient Q-T lengthening beyond normal limits. The peak CK level was significantly higher in patients with transmural infarction (1,256 ± 158 international units [IU]/liter) than in those with nontransmural infarction (349 ± 92 IU/liter) ($P < 0.001$). However, there was no significant difference between the presence of transient Q-T prolongation beyond normal limits in subjects with transmural (19 of 49, 39 percent) versus nontransmural (8 of 14, 57 percent) infarction.

Discussion

The results outline for the first time a "natural history" for the Q-T interval in the days after acute myocardial infarction. It is significantly lengthened relative to control values in days 1 through 4 (maximal on day 2) and returns almost to control level by day 14. In all

TABLE II

Q-Tc Interval 0 to 14 Days After Infarction (mean ± standard error of the mean with ranges) (in seconds)

Days After Infarction (no.)	Group A	Group B	Group C
0	0.403 ± 0.011 (0.358–0.451)	0.405 ± 0.006 (0.372–0.464)	0.404 ± 0.005 (0.358–0.464)
1	0.452 ± 0.013* (0.396–0.536)	0.430 ± 0.006† (0.353–0.515)	0.435 ± 0.005‡ (0.353–0.536)
2	0.481 ± 0.018† (0.406–0.642)	0.439 ± 0.006‡ (0.360–0.613)	0.448 ± 0.006‡ (0.360–0.642)
3	0.476 ± 0.018† (0.402–0.600)	0.435 ± 0.005‡ (0.365–0.502)	0.444 ± 0.006‡ (0.365–0.600)
4	0.441 ± 0.011* (0.375–0.486)	0.421 ± 0.006 (0.358–0.476)	0.427 ± 0.005† (0.358–0.486)
5	0.426 ± 0.012 (0.398–0.462)	0.418 ± 0.007 (0.356–0.461)	0.419 ± 0.006 (0.356–0.462)
6	0.416 ± 0.007 (0.388–0.436)	0.410 ± 0.009 (0.358–0.461)	0.413 ± 0.006 (0.358–0.461)
7–10	0.425 ± 0.010 (0.356–0.454)	0.409 ± 0.006 (0.360–0.458)	0.413 ± 0.006 (0.356–0.458)
11–14	0.412 ± 0.008 (0.343–0.450)	0.406 ± 0.006 (0.330–0.475)	0.407 ± 0.005 (0.330–0.475)

* Probability (P) value <0.05 versus day 0.
† $P < 0.01$ versus day 0.
‡ $P < 0.001$ versus day 0.
Group A = patients with nontransmural infarction; group B = patients with transmural infarction; group C = groups A and B combined.

patients whose Q-T interval lengthened beyond normal limits, regardless of the magnitude of prolongation, the Q-T duration returned to normal by day 6 after infarction. We used a single daily electrocardiogram to define change in the Q-T interval, but this measurement, particularly during the early hours of myocardial infarction, is frequently variable. An hour by hour study of the interval in the first 48 hours would add further definition.

The greater incidence of abnormal Q-T duration in patients with nontransmural infarction is consonant with the solid angle theory.[14] In this lesion (as opposed to transmural infarction) a larger injured/healthy boundary area confronts the facing unipolar electrode. Q-T prolongation in this instance may possibly prove to be a useful sign in the diagnostic separation of ischemia from actual necrosis, when the electrocardiogram shows only T wave inversion.

Causes of Q-T prolongation: Any hypothesis about the causes of Q-T prolongation in myocardial infarction not only must explain changes in the interval, but also should consider the time course of those changes. Possible causes are considered below.

Local hypothermia: Hypothermia prolongs the Q-T interval,[5] and local cooling can prolong the duration of the transmembrane action potential[15] with corresponding changes in the sequence of recovery.[16] Two to 4 minutes after the onset of coronary occlusion in the dog, there is a 0.5° C decrease in the temperature of the infarcted muscle compared with that of healthy tissue. From 10 minutes to 4 hours, there is little further decrease in temperature.[17] In irreversibly infarcted muscle the depression in temperature persists even after reperfusion.[18]

Local norepinephrine release or deprivation: Norepinephrine shortens the duration of the muscle action potential.[19] Hyperkalemia, local to an area of ischemia, can depolarize sympathetic nerve endings with release of norepinephrine.[20] On the other hand, ischemic neuronal death could deprive an injured zone of this catechol. Lengthening of the Q-T interval has been found with both bilateral sympathetic ablation and asymmetric sympathetic stimulation.[21–24]

Local conduction delay: Late start/finish of action potentials: Hypoxia, a component of ischemia, shortens action potentials.[25] Regional hyperkalemia, by its depolarizing effect, can delay conduction into the injured zone,[25,26] thus postponing local electrical systole. The registration of the latter in the QRS and Q-T intervals is a function of (1) the mass of tissue so delayed, (2) its temporal position in the sequence of activation, and (3) the amplitude of the upstrokes and the area under the recovery phase of the postponed action potentials. If the tissue mass is critically large or if conduction delay is severe or the infarct located in "final" (for example, posterobasal) portions of the activation sequence, the QRS duration will be expanded (periinfarction block). More commonly, the delayed upstrokes are of low voltage and temporally dispersed (even as late as the S-T segment[27]), and the QRS duration is thus normal. Although low voltage and dispersal may not permit sufficient collective effect to register as a terminal extension to the QRS interval, the collective effect of the combined areas under the action potential "shoulders" can easily register according to solid angle theory[14] as an extension of the Q-T interval.

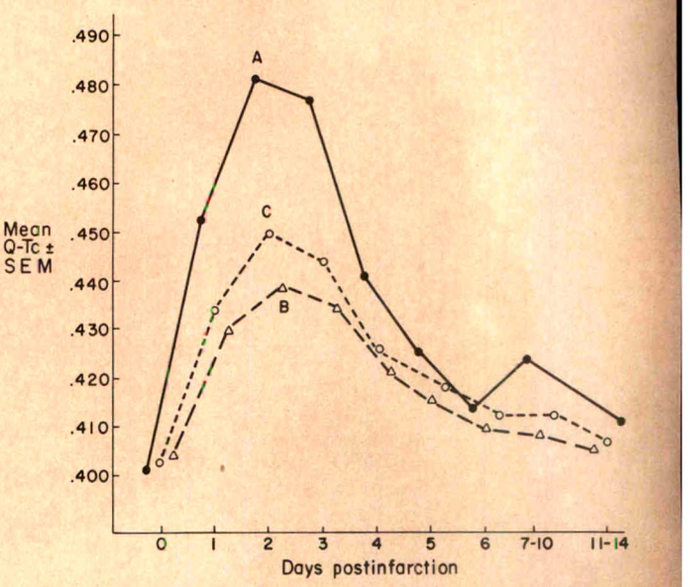


FIGURE 3. Time course of change in the corrected Q-T interval (Q-Tc) compared with preinfarction control values (day 0). A = patients with nontransmural infarction; B = patients with transmural infarction; C = groups A and B combined. SEM = standard error of the mean.

Local extracell hypocalcemia: Myocardial ischemia is nonuniform with respect to both severity and distribution.[28,29] Irreversibly injured cells can presumably influence the environment of their contiguous injured but viable neighbors.[30–32] Both reversibly[33,34] and irreversibly[35,36] injured myocardial cells take up, and even precipitate, in their mitochondria very large amounts of calcium. In condemned endothelial cells this process is accompanied by swelling, which may be sufficient further to diminish flow in the ischemic area, by compression. The process leads to electric uncoupling.[37] These events can induce local extracell hypocalcemia. In this milieu, prolonged action potentials would develop in the contiguous injured but excitable cells.

If a major contributing cause of Q-T prolongation in myocardial infarction is intracell calcium accumulation with resultant extracell hypocalcemia, the latter should be maximal, according to our data, on days 2 and 3 after infarction. A temporal and topographic relation between calcium accumulation and technetium-99m pyrophosphate uptake in acute myocardial infarction was demonstrated by Buja et al.[38] Their study and others[39–42] have shown that the uptake of this radionuclide increases progressively over the first 48 hours after infarction. Direct measurements of myocardial electrolyte content also show that calcium accumulation reaches its peak at 48 hours.[43] In most patients the radionuclide scintigrams have become normal by day 7 after infarction.[38–42] Thus, local hypocalcemia is an attractive possible cause of the time-related changes in the Q-T interval.

Because of the inhomogeneity of tissue disturbance in myocardial infarction, it is possible that all of the

preceding causes may be operative concomitantly or at different times during the hours or days after the onset of infarction. The sole reason for emphasizing hypocalcemia as a possible cause is the collateral evidence derived from nuclear imaging studies and from experimental pathologic data.

Clinical implications: Our study leaves as still conjectural the value of the Q-T measurement in (1) the crude "dating" of a myocardial infarction, (2) the numerical definition of the period of "electrical instability" (the relation of serious arrhythmia to dispersion in recovery time[44] theoretically suggests a positive correlation with Q-T expansion), and (3) evaluation of patients presenting with ischemia but without evidence of necrosis.

Acknowledgment

We thank Roger Holland and Ernest Page, MD.

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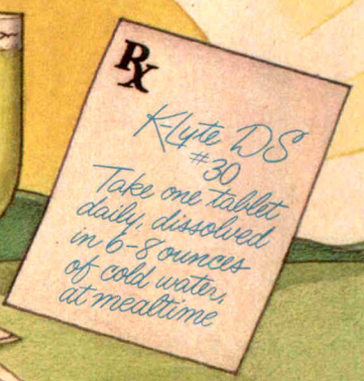
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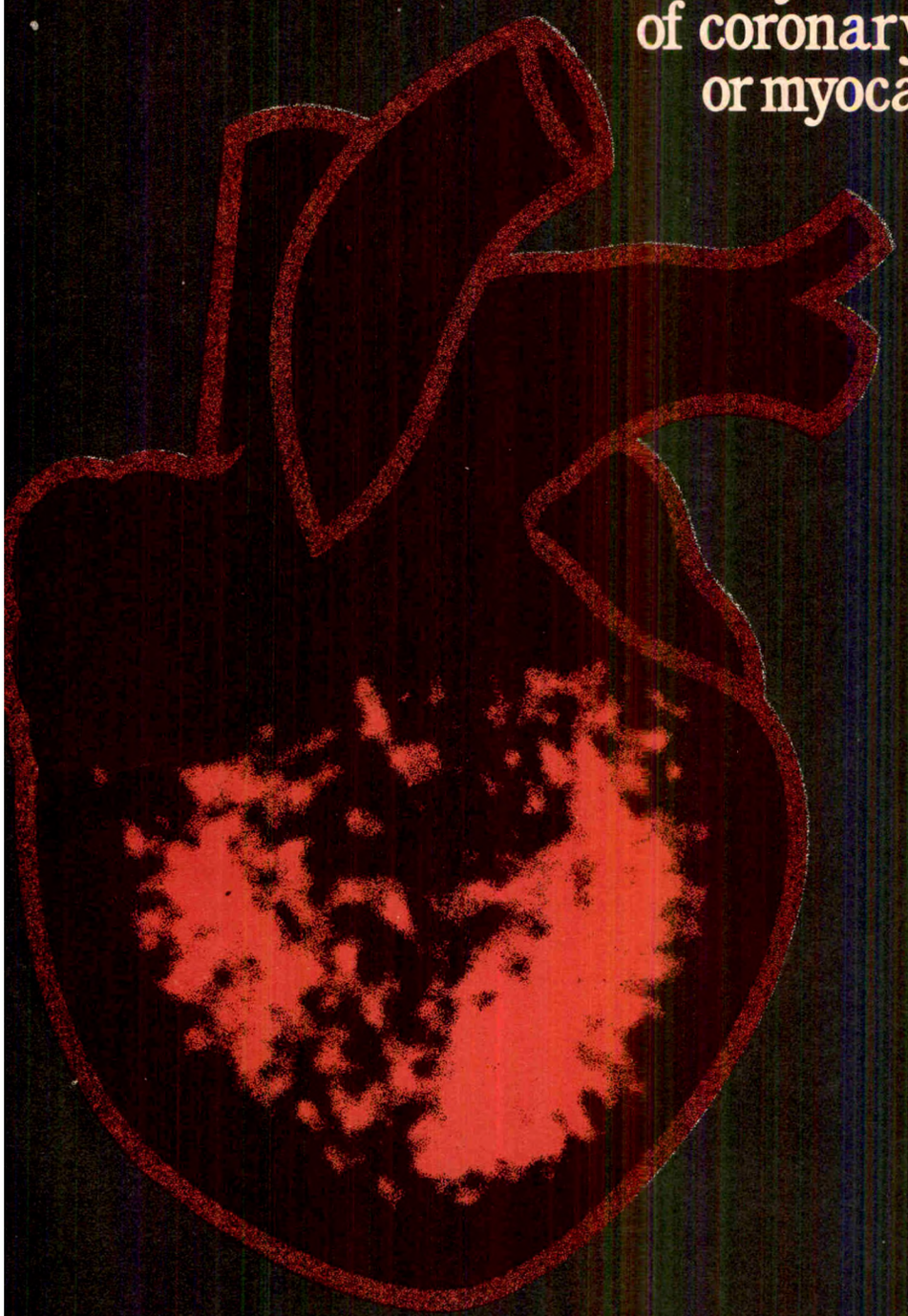
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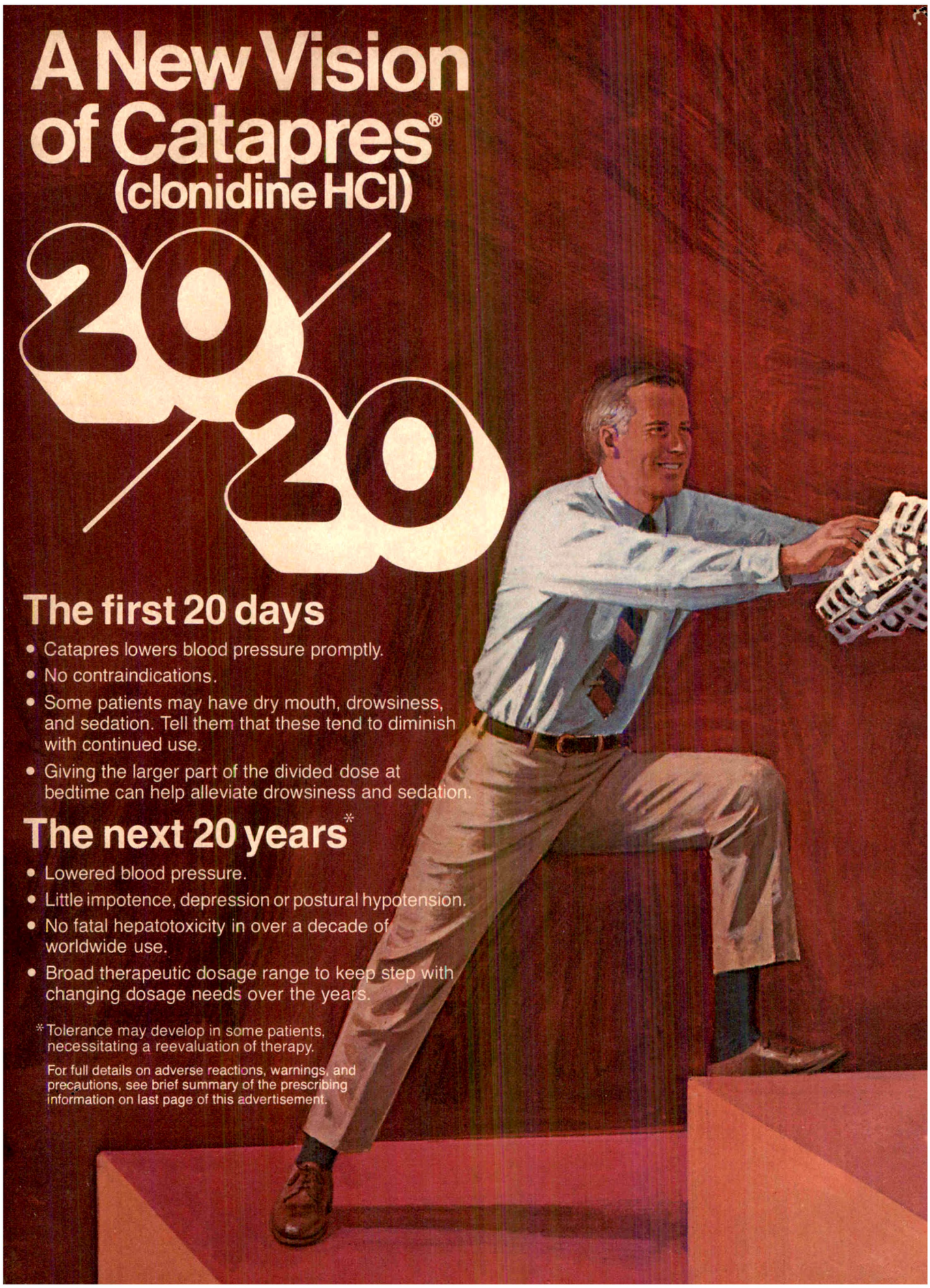
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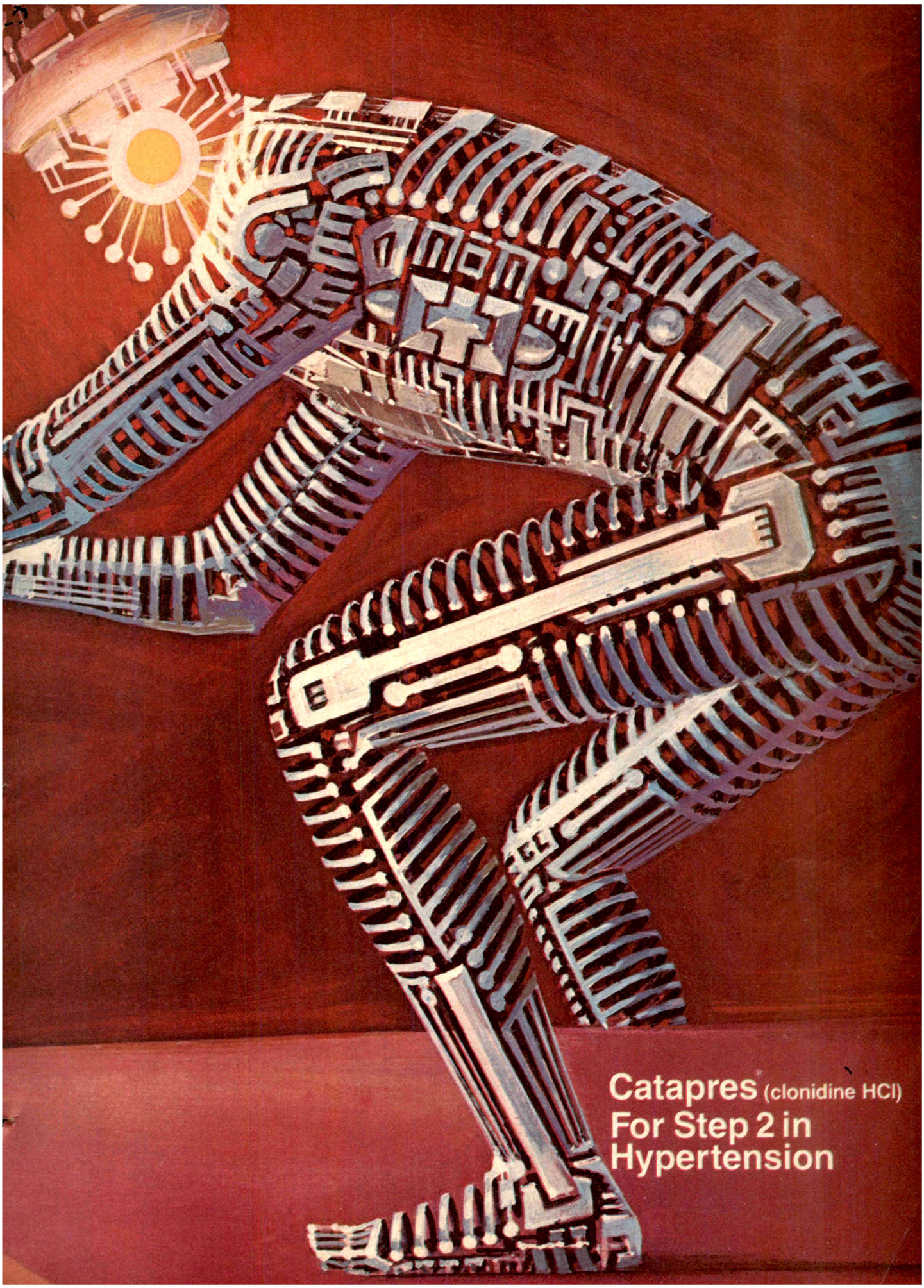
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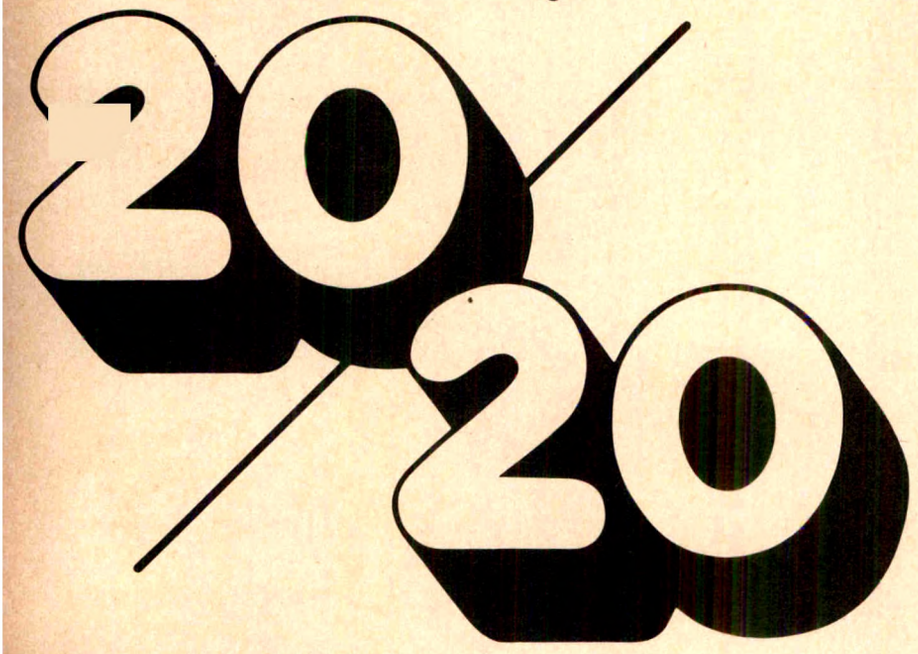



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Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone, and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000.

For complete details, please see full prescribing information.

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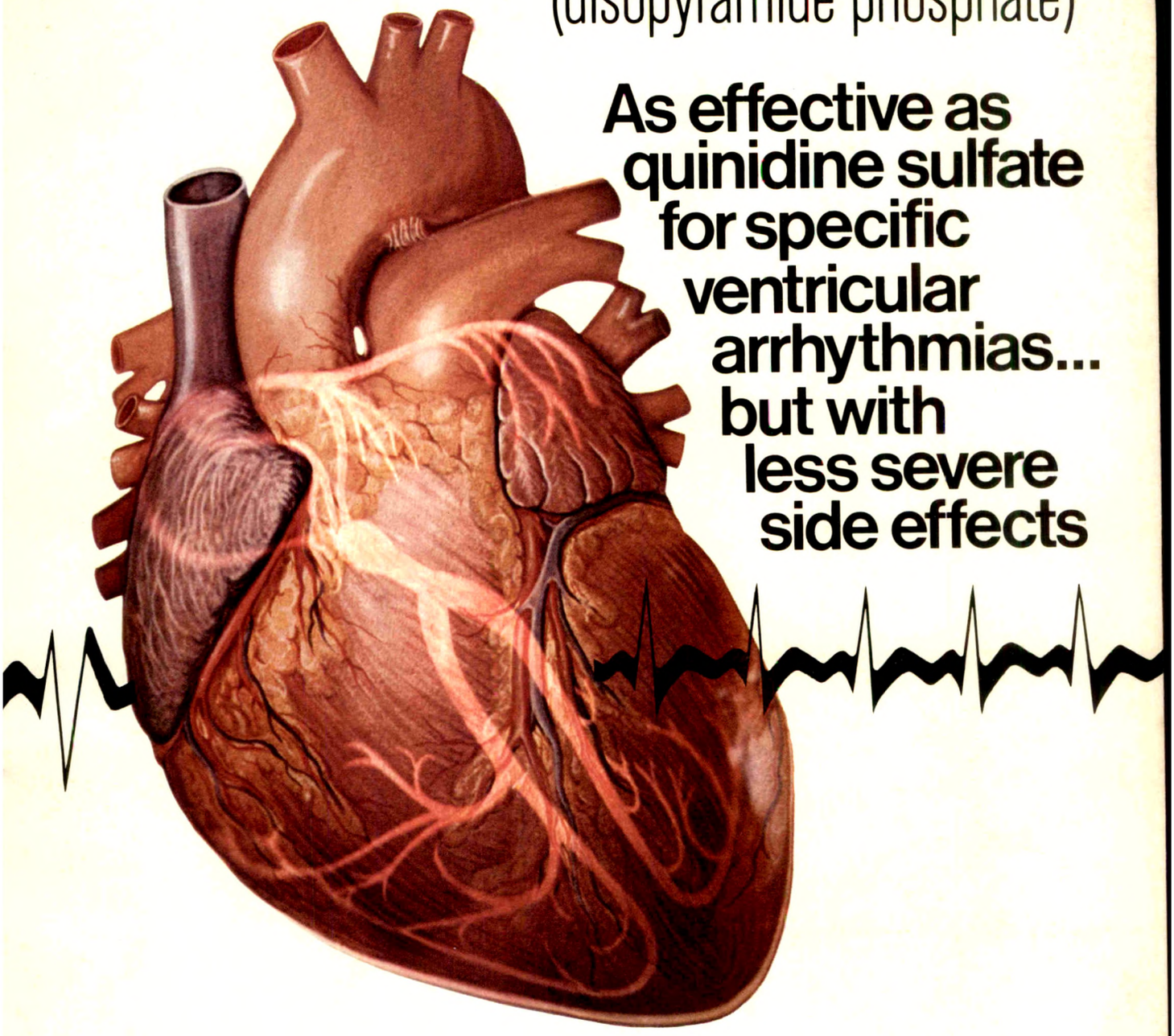
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JC-4

From Searle

Norpace®

(disopyramide phosphate)



As effective as quinidine sulfate for specific ventricular arrhythmias... but with less severe side effects

Efficacy thoroughly proved and documented—no other antiarrhythmic agent subjected to such rigidly controlled study prior to introduction

Effective in specific ventricular arrhythmias—indicated in premature ventricular contractions (PVCs): unifocal, multifocal or paired PVCs or episodes of ventricular tachycardia (VT)

Excellent patient tolerance—less severe side effects than quinidine . . . and significantly better tolerated

Dose-related plasma levels—plasma levels correlate closely with dosage

Minimal effect on hemodynamics—rarely alters blood pressure significantly at recommended oral doses, and may reduce cardiac output by about 10%

Please see last page for a brief summary of prescribing information.

In specific ventricular arrhythmias...provec

Norpace®

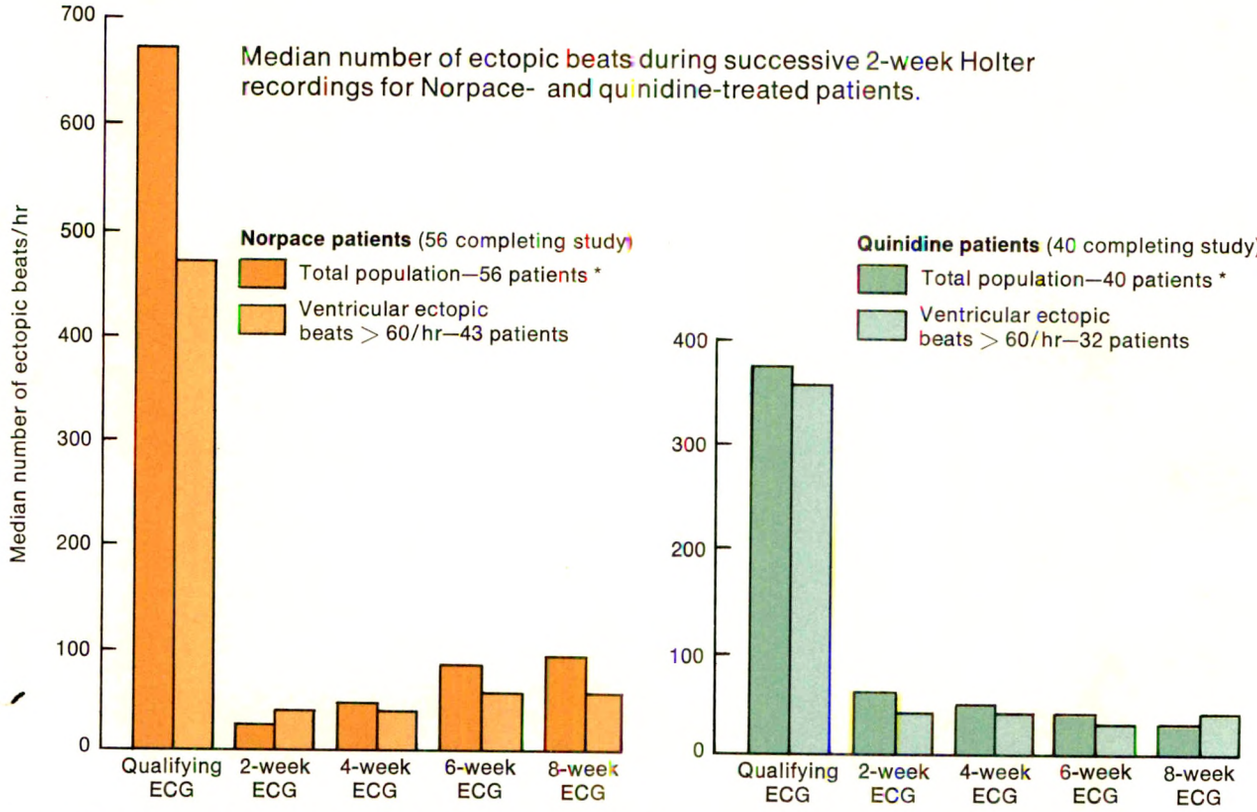
(disopyramide phosphate)

as effective as quinidine sulfate...

Results of double-blind controlled studies

A double-blind multicenter clinical study involving five investigators was conducted to compare the relative effectiveness and tolerance of Norpace and quinidine sulfate. Prior to qualifying for the study, each patient had antiarrhythmic medication discontinued for at least one week. Nine-hour Holter recordings were then used to establish an admission criterion of at least 60 ectopic beats per hour (PVCs, PACs or combination of the two). All other arrhythmias were excluded except paroxysmal ventricular or atrial tachycardias occurring in conjunction with the above. It was apparent that both drugs were capable of reducing ectopic activity and maintaining suppression throughout the course of therapy.

Median number of ectopic beats during successive 2-week Holter recordings for Norpace- and quinidine-treated patients.



* Includes patients with more than 60 total (atrial and ventricular) ectopic beats per hour but who had fewer than 60 ventricular ectopic beats per hour.

There was no statistically significant difference in reduction of ectopy between the two drugs.

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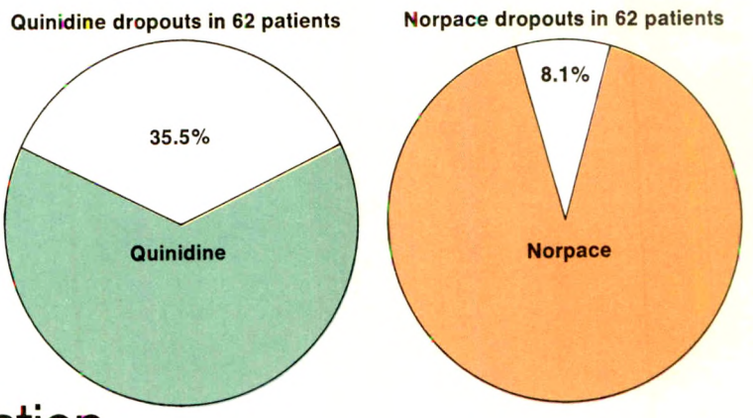
effective by extensive Holter monitoring

with less severe side effects

Significantly fewer dropouts with Norpace

(disopyramide phosphate)

The entire study population was analyzed for side effects. The side effects experienced by Norpace patients were usually mild and mainly anticholinergic, including: dry mouth, urinary hesitancy, constipation, blurred vision. The anticholinergic side effects were generally transient. Adverse reactions with quinidine were more serious and affected a greater number of patients. The most common symptoms were: severe diarrhea; gastrointestinal symptoms including cramps, nausea and vomiting; dizziness; fever; and rash.



Dosage and administration

Supplied as 100-mg and 150-mg capsules. Dosage should be individualized based on response and tolerance. Usual adult dosage is 400 to 800 mg per day given in divided doses four times daily, following an initial loading dose.

Recommended dosage regimen

Patient type	Loading dose	Maintenance dose
Adult	300 mg	150 mg q 6 h
Adults of smaller stature; or with moderate renal insufficiency, hepatic insufficiency, cardiomyopathy, or possible cardiac decompensation	200 mg	100 mg q 6 h
Adults with severe renal insufficiency C_{cr} less than 40 ml/min	200 mg	100 mg given approximately every half-life (see Note below)

Note: Since Norpace is excreted in the urine, renal insufficiency appreciably extends the half-life of the drug. The chart below provides guidelines to the appropriate Norpace dosage in such patients.

Norpace dosage interval adjustment for patients with renal insufficiency

Creatinine clearance (ml/min)	40-15	15-5	5-1
Approximate maintenance-dosing interval	q 10 h	q 20 h	q 30 h

Norpace plasma half-life may also be prolonged in patients with significant liver disease.

Please see next page for a brief summary of prescribing information.

SEARLE

Norpace®
(disopyramide phosphate)



as effective as quinidine sulfate for specific ventricular arrhythmias...with less severe side effects

Before prescribing Norpace, please consult complete prescribing information, a summary of which follows:

Indications: Norpace is indicated for suppression and prevention of recurrence of the following cardiac arrhythmias when they occur singly or in combination: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion).

Norpace is equally effective in treating the above arrhythmias in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease. Oral Norpace has not been adequately studied in patients with acute myocardial infarction or in patients with persistent ventricular tachycardia, atrial arrhythmias or arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established.

Contraindications: Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug.

Warnings: Severe hypotension has been observed on rare occasions, primarily in patients with primary cardiomyopathy or inadequately compensated congestive heart failure. If hypotension develops Norpace should be discontinued promptly unless it is due to the arrhythmia.

Norpace should not be used in the presence of poorly compensated or uncompensated congestive heart failure unless it is exacerbated by or caused by an arrhythmia and proper treatment including optimal digitalization has been accomplished. In some patients with marginally compensated heart failure, Norpace may cause cardiac decompensation. In these patients, progressing congestive heart failure should generally be treated with cardiac glycosides and diuretics and the course of treatment closely followed. Norpace dosage should be reduced or discontinued if adequate control of congestive failure is not attained.

If first-degree heart block develops, the dosage of Norpace should be reduced. If the block persists, continuation of Norpace must depend upon an assessment of the benefit versus the risk. Development of second- or third-degree AV block or uni-, bi- or trifascicular block requires discontinuation of Norpace, unless the ventricular rate is adequately controlled by a pacemaker.

Because of its anticholinergic properties, Norpace should not be used in patients with glaucoma or urinary retention, unless adequate overriding measures are taken.

Precautions: If significant widening (greater than 25%) of the QRS complex occurs, Norpace should be discontinued. If Q-T prolongation greater than 25% occurs and if ectopy continues, monitor closely and consider discontinuing Norpace.

Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits.

The effect of Norpace is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block.

Norpace should be administered cautiously to patients who are receiving or who have recently received other antiarrhythmic drugs. Excessive widening of the QRS complex may occur in such instances.

Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage.

Antiarrhythmic drugs may be ineffective in patients with hypokalemia. Therefore, any potassium deficit should be corrected before instituting Norpace therapy.

Use in Pregnancy and Lactation: Safe use in pregnancy has not been established. The use of Norpace in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus.

It is not known whether disopyramide is excreted in human milk. However, studies in rats have shown that the concentration of disopyramide and its metabolites is up to three times greater in milk than in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted.

Labor and Delivery: The effects of Norpace on the fetus during delivery or on the course of labor and delivery are unknown.

Pediatrics: The safety and effectiveness of Norpace in children have not been established.

Adverse Reactions: *Anticholinergic:* dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention. *Genitourinary:* urinary frequency and urgency, dysuria. *Gastrointestinal:* nausea, pain/bloating/gas, anorexia, diarrhea, vomiting. *Central Nervous System:* nervousness, depression, insomnia, impotence, dizziness, general fatigue/muscle weakness, headache, malaise, and rarely, reversible acute psychosis. *Cardiovascular:* edema/weight gain, cardiac conduction disturbances, shortness of breath, syncope, chest pain, hypotension. *Dermatologic:* generalized rash/dermatoses.

Dosage and Administration: Dosage must be individualized for each patient on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg per day given in divided doses four times daily, following an initial loading dose. The recommended initial dosage schedule for adults is a single loading dose of 300 mg, followed by 150 mg every six hours.

For patients of small stature, or for those with moderate renal insufficiency, hepatic insufficiency, cardiomyopathy, or possible cardiac decompensation, a loading dose of 200 mg is recommended, followed by 100 mg every six hours.

For patients with severe renal insufficiency lower doses are recommended. See complete prescribing information for details.

Overdosage: No specific antidote for Norpace has been identified; treatment of overdosage should be supportive. Overdosage might be expected to produce excessive widening of the QRS complex, worsening of congestive heart failure, hypotension, varying kinds and degrees of conduction disturbance, bradycardia and finally asystole. Obvious anticholinergic effects might also be observed. The electrocardiogram should be monitored and supportive therapy with vasopressors, sympathomimetics, cardiac glycosides and diuretics should be given as required. In vitro studies have demonstrated good dialyzability for disopyramide.

How Supplied: Capsules containing 100 mg or 150 mg of disopyramide base. Available in bottles of 100 capsules.

SEARLE

Searle Laboratories
Division of G. D. Searle & Co.
Box 5110, Chicago, Illinois 60680

7N2



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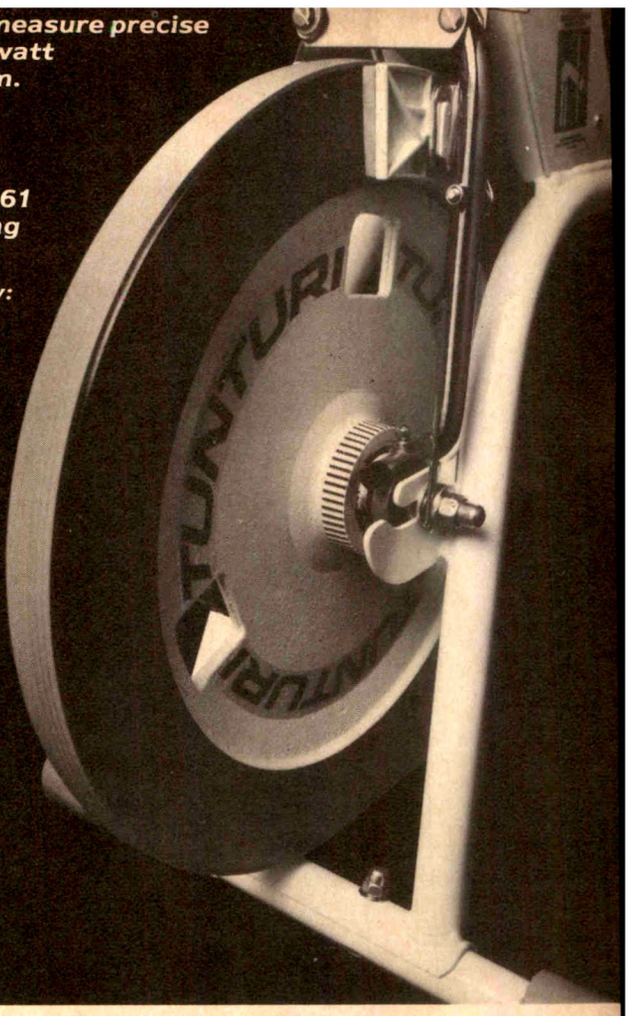
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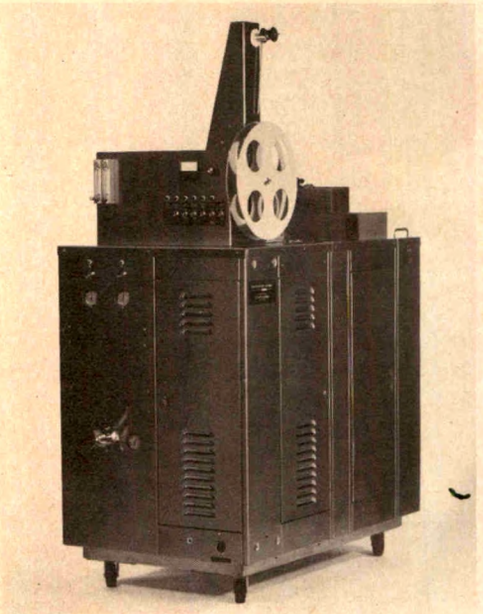


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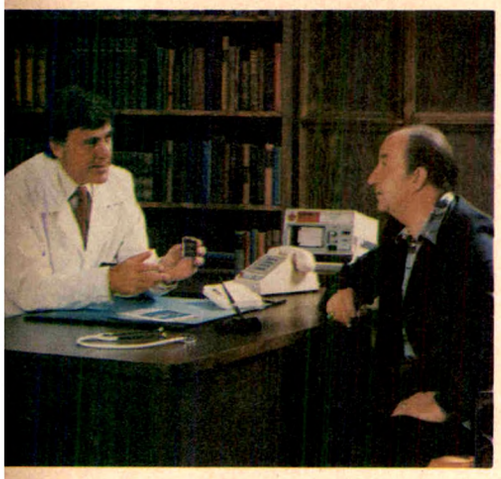
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Dallas, Texas 75235 Phone [214] 350-1283

JAMIESON FILM CO.
CINE FILM PROCESSORS

You've already earned your patient's confidence. We'd like to earn yours.



Confidence is reliability...
and reliability is the InterLith™



Your confidence in Intermedics is as important to us as your patient's confidence is to you. That's why we want you to know about the InterLith™, chosen around the world as one of the most reliable pacemakers available. Extensive use has confirmed its outstanding performance and reliability, resulting in an annual failure rate of only .003 at the 90% confidence level with no reported failures of its lithium power source. In addition to its proven reliability, the InterLith has significant features which make it an especially fine choice as a replacement pacemaker, such as a "universal" connector that readily accepts most leads without an adapter. So when your patient needs a pacemaker, for whatever reason, consider the InterLith, a pacemaker with which you can feel confident.

Confidence begins with extraordinary design features.

A tungsten inert gas (TIG) welding technique is used to hermetically seal the InterLith in a 316L stainless steel enclosure that prevents moisture leakage. A specially designed polycrystalline ceramic feedthrough seal, utilizing a 99.99% pure platinum conductor, makes the electrical connection to the pulse generator. The high collar design of the feedthrough minimizes fluid leakage in the harsh environment of the human body.

The InterLith is one of the smallest, lightest pacemakers on the market. Its corners are gently beveled, much as the contours of the patient's own body, minimizing the risk of pressure necrosis. The unipolar model weighs only 75 grams (80 grams for the bipolar) and measures 6.0 cm by 4.6 cm by 1.5 cm, enabling a smaller incision and a more cosmetic pocket for greatest patient comfort. The InterLith's bipolar and unipolar configurations provide the physician with a choice for every pacing situation.

Confidence increases with superior performance.

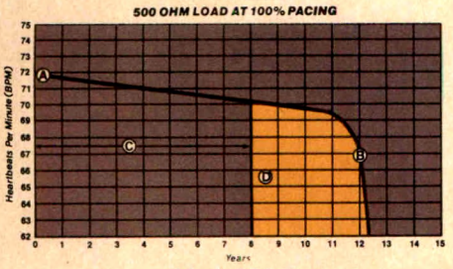
The InterLith's annual failure rate of less than .003 (at 90% confidence level) is largely attributable to the outstanding longevity of its lithium power cell, a battery without a single failure reported in 150,000 battery units manufactured. Combined with the proven reliability of c-mos circuitry, the InterLith provides superior performance at the lowest possible power consumption. This design represents sophisticated state-of-the-art technology in pacemaker electronics and gives the bipolar InterLith a theoretical longevity in excess of 11 years (12 years for the unipolar).*

Quality control insures confidence.

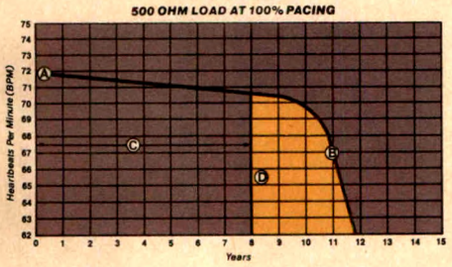
Every component utilized in the InterLith is selected and tested to meet the same standards as in the most exacting aerospace and military applications. Every step of the manufacturing process at Intermedics is subject to rigid quality assurance procedures in our complete environmental testing laboratory, because at Intermedics we believe only the highest quality products can merit your confidence. Some of the high reliability screening steps that our pacemakers receive in manufacturing are:

1. Twenty-four hour dynamic temperature cycling from −30° to +80° C.
2. Vibration testing at .1" displacement and 10 g's from 20 HZ to 2 KHZ.
3. Strip chart rate recording from 60° C.
4. Hermetic seal testing to 4×10^{-8} atm. cc/sec.

Model 223



Model 224



A. Beginning of Life Rate (Determined 6 months following implantation of pulse generator). B. End of Service Rate (Loss of 7% from Beginning of Life Rate) C. Assured Service Life. D. Possible Extended Life (Depending on current drain and projected battery performance).*

**Computed assuming a 500 ohm load and 100% pacing. Assuming a more typical 750 ohm load and 50% pacing, longevity for the model 224 and model 223 would increase to 20 years and 22 years, respectively.*

InterLith is a trademark of Intermedics, Inc., Freeport, Texas.



We put our confidence in the InterLith, and you can too.

Intermedics supports the outstanding reliability of the InterLith with a replacement credit agreement that will allow a replacement credit on any InterLith that fails for any reason within the first 96 months after implant.

Why not select the InterLith the next time one of your patients requires pacing therapy? Where reliability counts, there's no better choice.

Intermedics Inc.
P.O. Box 617
Freeport, Texas 77541

Our business is life.

Intermedics Pulse Generators

INDICATIONS FOR USE Pacemakers may be used in any application where asynchronous or demand ventricular pacing is indicated. These include congenital or acquired complete heart block which may be continuous or intermittent in nature, various types of sinus node dysfunction, WPW syndrome, carotid sinus hypersensitivity, drug induced bradycardia, and various ventricular arrhythmias.

The above list is not intended to be complete. The indications for pacing are increasing as the devices become more sophisticated and as methods for patient management become more widely understood.

PRECAUTIONS Implanted cardiac pacemakers have a finite service life and a relatively wide variability in service life. Factors affecting service life include the initial capacity of the battery and the shelf storage time of the manufactured pulse generator. Once implanted the anticipated service life of the generator is modified by variations in electrode system resistances, stimulation rate, and the percentage of time during which the pacemaker is inhibited. The current drain on the battery when inhibited is less than one-third of that when pacing with a typical lead installation. Other factors contributing to wide variability in service life are random electronic component failures.

All sensing pulse generators are inherently susceptible to magnetic electrical and electromagnetic fields. While design features are incorporated to minimize this susceptibility, an extraneous signal of sufficient strength and with characteristics which mimic normal cardiac activity can influence their operation. Additionally, certain environmental sources can couple sufficient energy into a cardiac pacemaker system to damage the pulse generator. Specifically, the implanting physician and the patient should be warned about the following:

(1) Electrocautery–Surgical use of electrocautery may cause temporary inhibition of the pulse generator. Additionally, pulse generator damage is possible if sufficient energy is coupled into it. Use of electrocautery within 4-5 centimeters of the implanted pacemaker can cause a direct coupling of RF energy through the lead and electrode to the cardiac muscle, producing burns or possible ventricular fibrillation.

Continuous monitoring of blood pressure and pulse should be instituted in all procedures where the use of electrocautery is contemplated. The ground plate of the electrocautery system should be placed in a manner to minimize current flow through the pacing system. A specific example is a TUR; during this procedure, the ground plate should be placed low on the buttocks or strapped to the thigh.

(2) Diathermy–A pacemaker patient should not receive this form of therapy. Very intense fields of microwave energy are involved and reactions of all sensing pulse generators are unpredictable. Total or virtually complete inhibition of the pacing circuitry is possible; however, no damage will result to the circuitry during the exposure.

(3) Microwave Ovens-Ovens, both in the home and in commercial use, in good condition and used as intended, or any microwave appliance which does not exceed federal guidelines of 0.5 milliwatts/cm² leakage at a point 2.5cm. from the appliance will not affect Intermedics pulse generators. However, appliances have been discovered which emit radiation in excess of 200 times these guidelines. The possibility of interference from such defective appliances does exist. The pulse generator will not be damaged by such exposure.

(4) Defibrillation–All implanted unipolar pulse generators regardless of manufacturer, can be damaged by cardiac defibrillation. Additionally, the presence of an implanted pacemaker system can increase the amount of cardiac muscle damage which results from defibrillation.

(5) Home Electrical and Gasoline Powered Appliances–Certain electrical and gasoline powered appliances can cause inhibition of an implanted cardiac pacemaker system. Pacemaker patients should be warned about the possibilities of pulse generator inhibition from some electric razors, most notably the rotary types, hand-held electric drills, power saws, and other appliances containing brush motors.

CONTRAINDICATIONS AND SIDE EFFECTS There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. The patient diagnosis and prognosis may indicate the type of pacemaker therapy used by the physician.

Body rejection phenomenon, local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism and cardiac tamponade have been reported from the use of implanted cardiac pacemakers.

Intermedics Inc.
P.O. Box 617 Freeport, Texas 77541

Peritrate® SA
Sustained Action
(pentaerythritol tetranitrate) **80 mg**

Peritrate®
(pentaerythritol tetranitrate) **40 mg**

Peritrate®
(pentaerythritol tetranitrate) **20 mg**

Peritrate®
(pentaerythritol tetranitrate) **10 mg**

CAUTION: Federal law prohibits dispensing without pre
Description: Each tablet of Peritrate SA Sustained Acti
pentaerythritol tetranitrate 80 mg (20 mg in immediate
and 60 mg in sustained release base). Each tablet of P
contains pentaerythritol tetranitrate 40 mg. Each tablet
20 mg contains pentaerythritol tetranitrate 20 mg. Each
Peritrate 10 mg contains pentaerythritol tetranitrate 10
(pentaerythritol tetranitrate) is a nitric acid ester of a te
alcohol (pentaerythritol).

Indications: Based on a review of this drug by the N
Academy of Sciences–National Research Council
other information, FDA has classified the indications
follows:

"Possibly" effective: Peritrate (pentaerythritol tetra
indicated for the relief of angina pectoris (pain asso
coronary artery disease). It is not intended to abort
anginal episode but it is widely regarded as useful in
phylactic treatment of angina pectoris.

Final classification of the less-than-effective indica
requires further investigation.

Contraindications: Peritrate SA Sustained Action (pent
tetranitrate) 80 mg and Peritrate (pentaerythritol tetrani
contraindicated in patients who have a history of sensi
drug.

Warning: Data supporting the use of Peritrate (pentaer
nitrate) during the early days of the acute phase of myo
infarction (the period during which clinical and laborat
are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to no
nephrine, acetylcholine, histamine, and many other ag

Precautions: Should be used with caution in patients w
glaucoma. Tolerance to this drug, and cross-tolerance
nitrites and nitrates may occur.

Adverse Reactions: Side effects reported to date have
dominantly related to rash (which requires discontinua
cation) and headache and gastrointestinal distress, wh
usually mild and transient with continuation of medicati
cases severe, persistent headaches may occur.

In addition, the following adverse reactions to nitrate
pentaerythritol tetranitrate have been reported in the lit

(a) Cutaneous vasodilatation with flushing.
(b) Transient episodes of dizziness and weakness, as
other signs of cerebral ischemia associated with
hypotension, may occasionally develop.
(c) An occasional individual exhibits marked sensitivi
hypotensive effects of nitrite and severe response
vomiting, weakness, restlessness, pallor, perspira
lapse) can occur, even with the usual therapeutic
Alcohol may enhance this effect.

Dosage: Peritrate (pentaerythritol tetranitrate) may be a
in individualized doses up to 160 mg a day. Dosage can
at one 10 mg or 20 mg tablet q.i.d. and titrated upward
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or one hour after meals and at bedtime. Alternatively, P
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tablets in bottles of 100 (N 0047-0001-51) and 1000 (N 0
Also unit dose, package of 10 x 10 strips (N 0047-0001-1

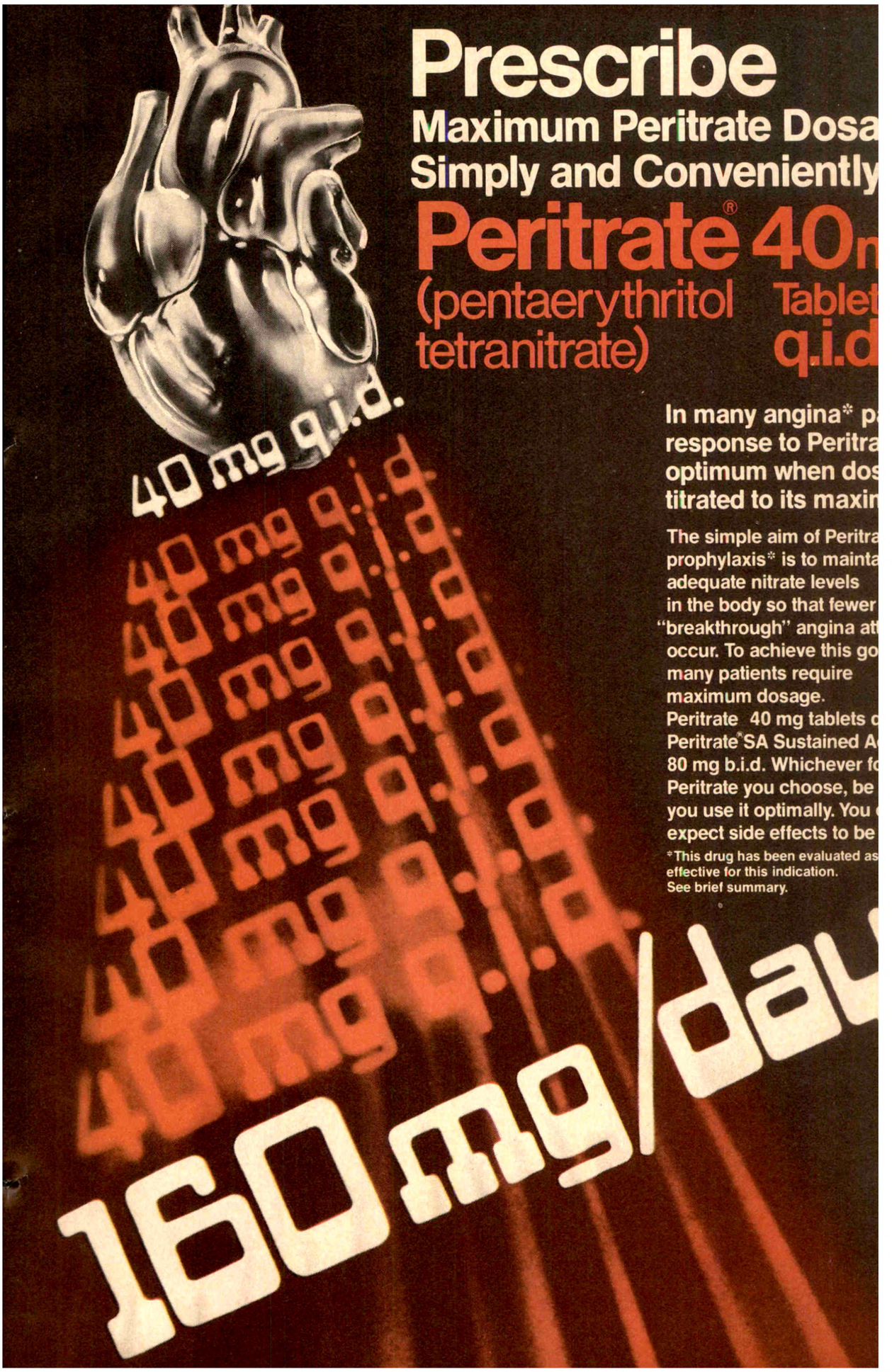
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significantly larger number of survivors in the drug-trea
Damage to myocardial tissue in the drug-treated surviv
extensive than in the untreated group. Studies in dogs
oligemic shock through progressive bleeding have dem
that Peritrate (pentaerythritol tetranitrate) is vasoactive
arteriolar level, producing increased blood flow and be
perfusion. These animal experiments cannot be translat
drug's actions in humans.

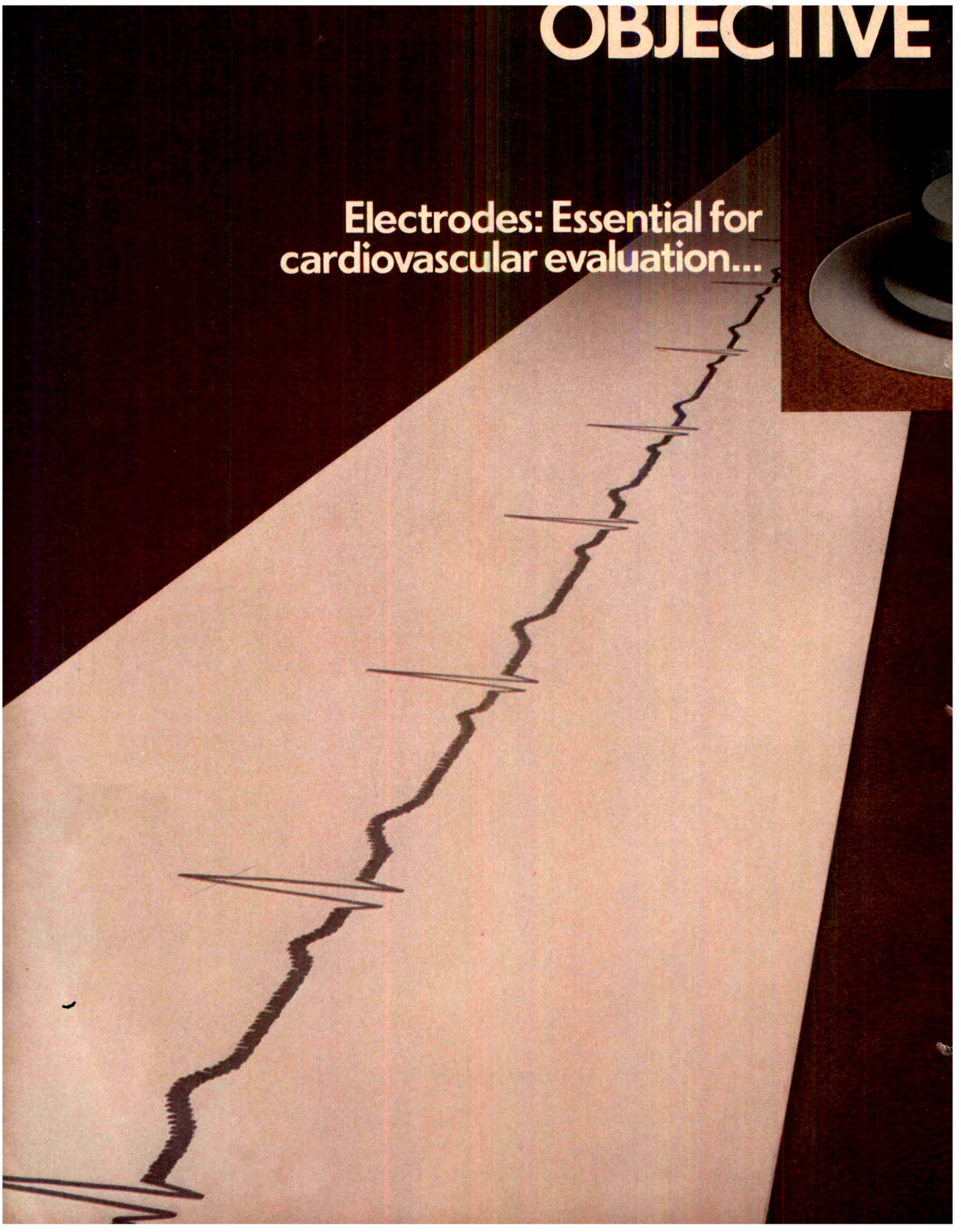
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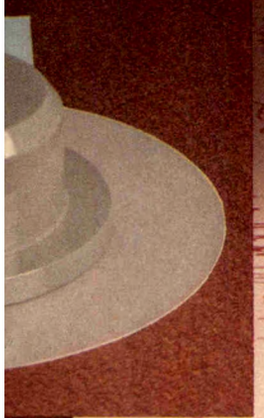
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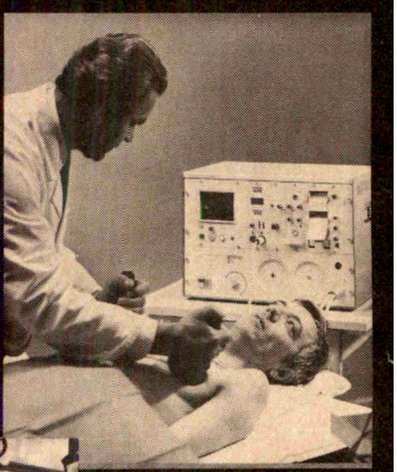
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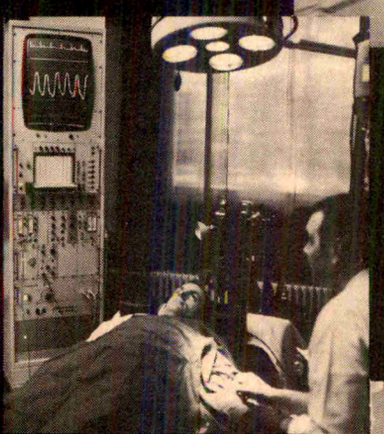
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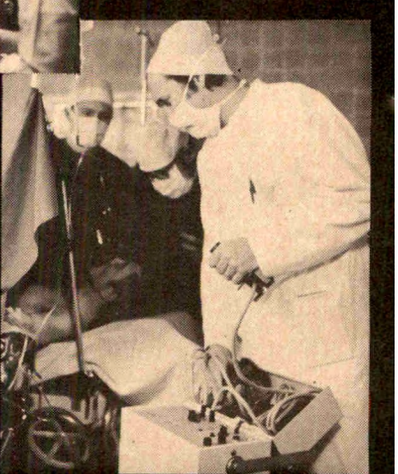
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Improvement by Propranolol of Regional Myocardial Dysfunction and Abnormal Coronary Flow Pattern in Conscious Dogs With Coronary Narrowing

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La Jolla, California

The effects of propranolol on regional myocardial function and the pattern of coronary blood flow velocity were studied during partial coronary arterial constriction in conscious resting dogs. Miniature ultrasonic crystals were implanted subendocardially in the left ventricle for measurement of segment length in control and ischemic areas. Coronary blood flow was limited by inflation of an hydraulic-cuff around the left circumflex coronary artery to produce stable hypofunction in the ischemic segment. With coronary stenosis, which reduced mean flow by an average of 31 percent of the control value, the heart rate increased by 17 beats from 78 ± 4 beats/min (mean ± standard error of the mean) and the flow pattern changed from a dominant diastolic to a dominant systolic pattern (peak velocity ratio of systole to diastole, 0.35 ± 0.06 to 1.06 ± 0.09) without change in left ventricular systolic pressure. After administration of propranolol (0.5 mg/kg intravenously), heart rate decreased to 72 ± 4 from 95 ± 4 beats/min and contraction in the ischemic segment increased markedly, as did left ventricular wall thickening. Simultaneously, coronary flow returned to a normal velocity pattern. These favorable effects were only partially diminished by cardiac pacing to increase the heart rate to that before treatment with propranolol. This study provides evidence for a substantial beneficial effect of propranolol when myocardial dysfunction results from transient coronary arterial stenosis, and it suggests several mechanisms that may be operative under these conditions.

The favorable influence of beta adrenergic blockade on angina pectoris in patients with coronary heart disease is well documented,[1,2] but controversy remains concerning the relative effects of propranolol on oxygen usage, coronary blood flow and contractile function in partially ischemic areas. Previous experimental studies from this laboratory[3,4] demonstrated beneficial effects of propranolol on regional myocardial function in marginal regions after acute coronary occlusion, but not in the central ischemic zone. Such changes in function of the marginal segment were of particular interest because this zone may be composed of partially ischemic cells or a mixed population of normal and ischemic cells[5,6]; however, the effects of propranolol on this region after complete coronary occlusion may not be directly relevant to conditions in angina pectoris, where partial flow is usually maintained through a stenotic coronary artery. Therefore, we studied the effects of propranolol on regional myocardial function and the pattern of coronary blood flow in conscious dogs, in which stable myocardial hypokinesia was produced acutely with partial inflation of a cuff occluder on the left circumflex coronary artery.

From the Division of Cardiology, Department of Medicine, University of California, San Diego School of Medicine, and the Scripps Clinic and Research Foundation, La Jolla, California. This project was supported by Grants HL 17682 and HL 12373 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received June 22, 1977; revised manuscript received October 17, 1977, accepted October 19, 1977.

Address for reprints: John Ross, Jr., MD, Division of Cardiology, Department of Medicine, M-013, University of California, San Diego, La Jolla, California 92093.

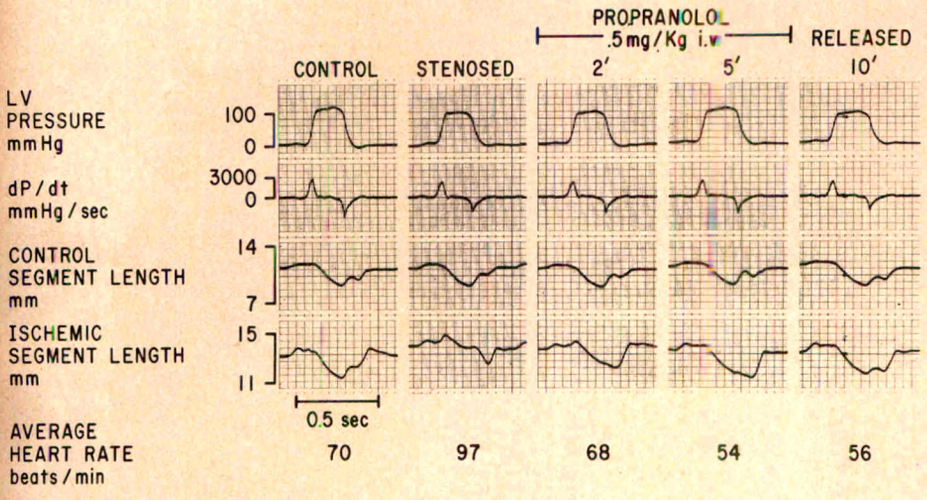


FIGURE 1. Effects of partial coronary constriction and propranolol on regional myocardial function in the conscious dog. Left ventricular (LV) pressure and its first derivative (dP/dt) and control and ischemic segment dynamics are shown. The control segment shows a slight increase in the extent of shortening after coronary stenosis followed by slight reduction in shortening after propranolol (at 5 minutes). In the ischemic segment, early bulging and hypokinesia initially occur, but as heart rate decreases after propranolol the extent of shortening is increased. By 10 minutes after release of the stenosis, shortening patterns have returned to normal. Note that protodiastolic shortening observed in the ischemic segment 5 minutes after propranolol has disappeared subsequent to complete release of the hydraulic cuff. i.v. = intravenously.

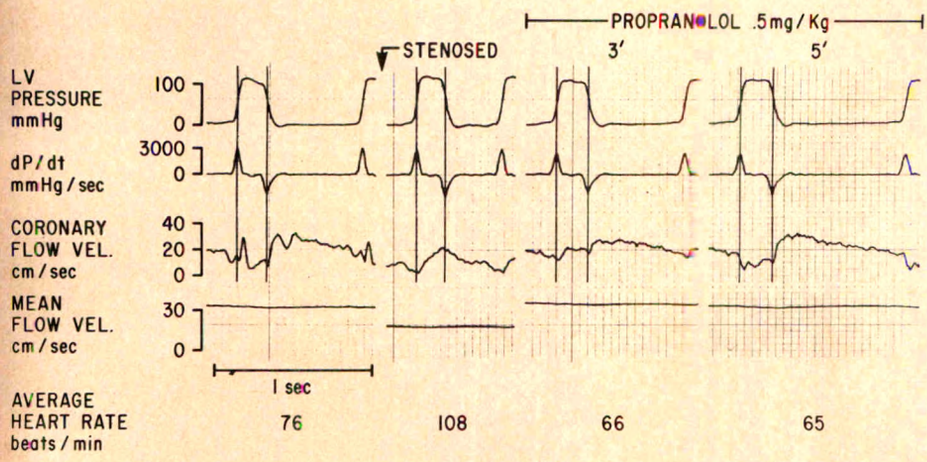


FIGURE 2. Changes in coronary blood flow patterns after coronary stenosis followed by propranolol administration. Left ventricular (LV) pressure, dP/dt, coronary flow velocity (VEL.) and mean flow velocity are recorded simultaneously. Note that the coronary blood flow velocity has changed from diastolic flow dominance to systolic flow dominance during coronary narrowing. This pattern gradually changes toward a normal flow pattern after propranolol administration.

Methods

Experimental preparation: Seven mongrel dogs weighing 24 to 38 kg were anesthetized with pentobarbital sodium (25 mg/kg body weight intravenously). After left thoractomy and pericardiotomy, a high fidelity micromanometer (Konigsberg P-22) was implanted in the left ventricular chamber through a stab incision at the apex. Pacing electrodes were sutured to the right atrial appendage. The circumflex coronary artery was dissected free near its origin, a hydraulic cuff was placed around it and a miniaturized 10 megahertz Doppler flow probe was placed proximal to the cuff.[7–9] A flowmeter signal satisfactory for analysis was obtained in six of the dogs. Stainless steel wire was used for electrical connections to the transducers to minimize torque on the blood vessel and wire breakage due to prolonged cyclic flexure.

For the measurement of regional myocardial function, two pairs of miniature 5 megahertz ultrasonic crystals were positioned in the left ventricular wall in a circumferential plane close to the endocardium, each pair separated by 1 to 1.5 cm as previously described.[4] One pair of crystals was placed in the wall near the base of the posterior papillary muscle in the distribution of the circumflex coronary artery (ischemic segment); the other pair was placed in the anterior wall of the left ventricle (normal segment). In all seven dogs signals from the normal segments were satisfactory, and tracings were obtained from the ischemic segment in six dogs. In five of the seven

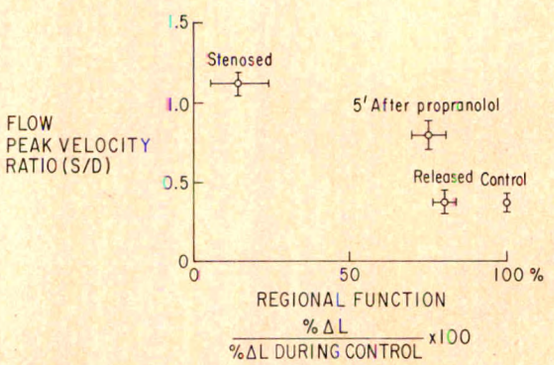


FIGURE 3. Average of relations between the ratio of peak coronary blood flow velocity in systole (S) and diastole (D) and associated myocardial function in the ischemic region in six dogs. Data are expressed as percent change of percent shortening of segment length (% ΔL) with percent shortening during the control period being considered 100 percent. During the control period, before coronary stenosis, $V_{S/D}$ is low, averaging 0.35 ± 0.06 (mean ± standard error). With coronary stenosis, systolic flow becomes dominant and ischemic segment shortening has decreased to 11 percent of the control value. After propranolol, $V_{S/D}$ decreases toward the control value and ischemic segment shortening returns to 75 percent of the control level. Data obtained 10 minutes after release of the coronary narrowing are also shown. In each dog the more depressed regional function from ischemic segment and ischemic wall thickness measurements was selected for representation in this figure.

dogs, two pairs of crystals were also placed at the endocardium and the epicardium in the control and ischemic areas to measure wall thickness, as described previously.[10,11]

Protocol: Studies were conducted in dogs lying quietly awake or spontaneously asleep on the floor at least 10 days after operation when they were healthy and afebrile and had a resting heart rate of less than 90 beats/min. After control resting recordings, the water-filled hydraulic cuff was inflated gradually with a vernier screw-driven occluder syringe, while the left circumflex coronary blood flow and the segment shortening pattern were monitored. With gradual adjustment (10 to 15 minutes) of the occluder, it was possible to achieve a state of stable segment hypofunction intermediate between full bulging and normal shortening[3,4] (Fig. 1). Mean coronary blood flow velocity had decreased by an average of 31 percent at this level of hypokinesia. Once this state was achieved, the occluder was not manipulated for the remainder of the experiment. Stable regional dysfunction was verified by observation for 4 to 7 minutes (average 5.1); because flow and segment function could not be recorded simultaneously, we assumed a stable state from observation of segment function, and flow was recorded only at the onset and end of the induction of partial stenosis. Propranolol, 0.5 mg/kg, was then administered intravenously over 3 minutes, and a 5 minute period then ensued to insure stability before the effects of propranolol were measured. If instability or excitement of the dog was observed, the control data were discarded and after at least a 30 minute wait another control period was initiated. Sometimes studies were postponed until the next day. In other studies utilizing the same experimental preparation but requiring longer periods of constant partial constriction, the hypokinetic state was sustained for up to 3 hours. After these measurements, atrial pacing was conducted for 2 minutes at the same heart rate measured during coronary constriction before administration of propranolol. The hydraulic cuff was then released.

Analysis of measurements: Recordings were monitored on a multichannel recorder and stored on magnetic tape for subsequent replay and analysis. Left ventricular pressure was recorded continuously, but alternating measurements of coronary blood flow velocity and segment dimensions were made because the electronics of the flow and dimension measuring systems precludes simultaneous measurements. The micromanometer was calibrated in vitro against a mercury manometer before implantation. Before and after each study the micromanometer was calibrated electrically, and upon replay of the tape before analysis the electrical pressure calibration was matched with values obtained previously with use of a mercury manometer. At autopsy the calibration was again verified in vitro with a mercury manometer.

The variables analyzed included peak systolic and end-diastolic left ventricular pressures, first derivatives of left ventricular pressure (dP/dt), regional dimensions and their first derivatives (dL/dt) and analog calculations of an index of segment work per beat $\int(P \times dL/dt)dt$ and per minute (stroke work × heart rate), where P = pressure and L = segment length. The tension-time index was calculated as the area under the left ventricular pressure curve using an analog integrator resetting at peak dP/dt. The values for segment length and wall thickness were normalized to a 10 mm initial length[3] by dividing the end-diastolic and end-systolic dimensions by the control end-diastolic dimensions and multiplying by 10.

Calibration of the Doppler flow velocity recording was conducted by injecting signals of known frequency into the zero-cross counter; flow velocity was then calculated from the Doppler equation.[8,9] The ratio of systolic to diastolic flow was determined with manual integration using a Tektronix electrical planimeter; peak velocity values were averaged over several cycles, and brief transient spikes such as the one in early systole in Figure 2 were excluded.

Data used for analysis were recorded at a paper speed of 100 mm/sec and averaged over 10 cardiac cycles. Paired data were used in the statistical analysis of hemodynamic and regional dimension data using a correction for multiple *t* tests, statistical significance being taken as a probability (*P*) value equal to or less than 0.025.[12] A *P* value less than 0.05 was considered borderline. The data in the text and figures are expressed as mean ± standard error of the mean.

Results

The hemodynamic and segment function data are summarized in Table I. The responses were directionally similar in all seven dogs, and representative tracings showing alterations in regional segment function and coronary flow are reproduced in Figures 1 and 2. Sequential changes in systolic/diastolic coronary flow ratios are correlated with changes in regional function in Figure 3 and the coronary flow data are summarized

TABLE I

Effects of Coronary Stenosis and Propranolol on Hemodynamic Variables and Regional Myocardial Function

	Control	Stenosis (*P*-1)	Propranolol (*P*-2)
Hemodynamics (no. = 7)			
Heart rate (beats/min)	78 ± 4	95 ± 4 ($P < 0.01$)	72 ± 4 ($P < 0.01$)
LVSP (mm Hg)	112 ± 4	111 ± 5 (NS)	118 ± 3 (NS)
LVEDP (mm Hg)	8.6 ± 0.9	11.4 ± 1.5 (NS)	13.0 ± 1.2 (NS)
LV dP/dt (mm Hg/sec)	2982 ± 71	2737 ± 16 ($P < 0.05$)	2618 ± 94 (NS)
TTI (mm Hg·sec/min)	1428 ± 66	1720 ± 103 ($P < 0.05$)	1444 ± 89 (NS)
Control segments (no. = 7)			
EDL (mm)	10.00	10.03 ± 0.05 (NS)	10.05 ± 0.06 (NS)
% ΔL	21.7 ± 2.2	22.0 ± 2.5 (NS)	19.9 ± 2.4 ($P < 0.01$)
Peak velocity (cm/sec)	1.72 ± 0.20	1.72 ± 0.21 (NS)	1.57 ± 0.20 ($P < 0.01$)
Stroke work ($\times 10^4$ dynes·cm)	2.53 ± 0.28	2.38 ± 0.31 (NS)	2.17 ± 0.23 (NS)
Minute work ($\times 10^4$ dynes·cm)	196 ± 24	225 ± 29 (NS)	157 ± 19 ($P < 0.025$)
Ischemic segments (no. = 6)			
EDL (mm)	10.00	10.17 ± 0.06 ($P < 0.05$)	10.17 ± 0.09 (NS)
% ΔL	14.6 ± 1.7	5.2 ± 0.8 ($P < 0.01$)	11.8 ± 1.3 ($P < 0.01$)
Stroke work ($\times 10^4$ dynes·cm)	1.87 ± 0.20	1.01 ± 0.18 ($P < 0.01$)	1.92 ± 0.10 ($P < 0.01$)
Minute work ($\times 10^4$ dynes·cm)	146 ± 18	94 ± 17 ($P < 0.01$)	141 ± 10 ($P < 0.025$)

All values are expressed as mean ± standard error of the mean.
EDL = end-diastolic length; HR = heart rate; LV dP/dt = peak positive first derivative of left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; LVSP = peak left ventricular systolic pressure; NS = not significant; *P*-1 = probability (comparison with control segment); *P*-2 = probability (comparison with stenosis); % ΔL = percent shortening; TTI = tension-time index.

TABLE II

Changes in Coronary Blood Flow After Coronary Stenosis and Propranolol (six dogs)

	Peak Systolic Flow (cm/sec)	Peak Diastolic Flow (cm/sec)	S/D Velocity Ratio	S/D Flow Ratio	Mean Total Flow Change (%)
Control	13.0 ± 3.1	36.9 ± 4.5	0.35 ± 0.06	0.13 ± 0.02	100
Stenosis	20.1 ± 2.1	19.3 ± 2.1	1.06 ± 0.09	0.59 ± 0.17	69.2 ± 14.1
(*P*-1)	(NS)	$P < 0.01$	$P < 0.01$	($P < 0.05$)	(NS)
Propranolol	24.9 ± 3.5	31.4 ± 1.5	0.79 ± 0.09	0.27 ± 0.05	110.5 ± 16.4
(*P*-2)	(NS)	($P < 0.05$)	($P < 0.05$)	(NS)	($P < 0.05$)

All values are expressed as mean ± standard error of the mean.
NS = not significant; *P*-1 = probability (comparison with control); *P*-2 = probability (comparison with stenosis); S/D = systolic/diastolic.

in Table II. Table III summarizes the changes in segment wall thickness.

Effects of Acute Coronary Arterial Stenosis

Coronary blood flow responses: With partial inflation of the cuff around the circumflex coronary artery sufficient to produce stable hypokinesia the coronary blood flow pattern changed drastically (Fig. 2). The peak diastolic velocity decreased after coronary stenosis by an average of 48 percent of control value, from 37 to 19 cm/sec ($P < 0.01$), whereas the systolic flow velocity increased (Table II). The ratio of peak flow velocity during systole and diastole ($V_{S/D}$) increased from 0.35 to 1.06 and the average flow ratio ($F_{S/D}$) increased from 0.13 to 0.59. Mean coronary flow decreased to 69 percent of control value (Table II).

Hemodynamic changes: During stable hypokinesia of the ischemic segment produced by partial coronary constriction, the heart rate was higher than the control rate by an average of 17 beats/min (Table I). Left ventricular end-diastolic pressure tended to increase and peak dP/dt to decrease, but these changes were not significant. No significant change in left ventricular systolic pressure was observed; an increase in tension-time index was of borderline significance (Table I).

Regional myocardial function: During stable coronary stenosis, ischemic segment end-diastolic length increased by an average of 0.17 mm (1.7 percent) of control value, percent shortening decreased from 14.6 to 5.2 percent (Fig. 1) and regional stroke work decreased proportionally (Table I). There were no significant changes in control segment lengths and function (Fig. 1, Table I).

Correlation of the changes in ischemic segment function with the flow velocity ratios (Fig. 3) demonstrated the simultaneous occurrence of regional dysfunction with marked alteration in coronary flow pattern.

Effects of Propranolol

Coronary blood flow responses: Five minutes after 0.5 mg/kg of propranolol was administered, peak diastolic velocity increased from 19 to 31 cm/sec, and peak systolic velocity increased slightly but not significantly, from 20 to 25 cm/sec (Fig. 2). In all dogs, $V_{S/D}$ and $F_{S/D}$ ratios decreased; the peak $V_{S/D}$ ratio changed from 1.06 to 0.79 and the $F_{S/D}$ ratio from 0.59 to 0.27. Mean flow velocity increased from 69 to 111 percent of control value (Table II).

Hemodynamic responses: After the administration of propranolol heart rate decreased by 23 ± 5 beats/min, left ventricular systolic pressure was unchanged and end-diastolic pressure increased insignificantly (Table

TABLE III

Changes in Wall Thickness After Coronary Stenosis (CS) and Propranolol (P) (five dogs)

	Control Segment EDWth (mm)	Control Segment % ΔWth	Ischemic Segment EDWth (mm)	Ischemic Segment % ΔWth
C	10.00	20.1 ± 3.2	10.00	21.2 ± 4.1
CS	9.92 ± 0.09	20.4 ± 4.5	10.01 ± 0.16	0.9 ± 2.7
P-1	(NS)	(NS)	(NS)	$P < 0.01$
P	9.90 ± 0.06	18.7 ± 3.3	9.96 ± 0.15	13.4 ± 4.7
P-2	(NS)	(NS)	($P < 0.05$)	$P < 0.025$

All values are expressed as mean ± standard error of the mean.
C = control; EDWth = end-diastolic wall thickness; % ΔWth = percent systolic wall thickening; *P*-1 = probability (comparison with control); *P*-2 = probability (comparison with stenosis).

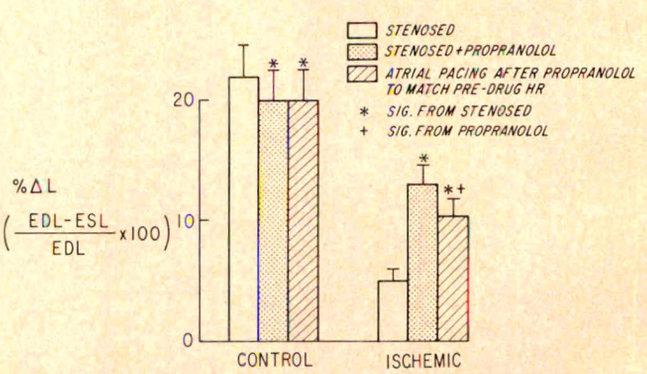


FIGURE 4. Effects of coronary arterial stenosis followed by administration of propranolol, and then by atrial pacing to produce a heart rate (HR) matched to the level existing before propranolol, on regional myocardial function. Data are expressed as percent change of percent segment shortening (% ΔL). The **bars at left** show responses in normal (control) segments; those **at right** show responses in the ischemic segments. * = $P < 0.02$; + = $P < 0.01$. EDL and ESL = end-diastolic and end-systolic segment length, respectively; Sig. = significance of difference.

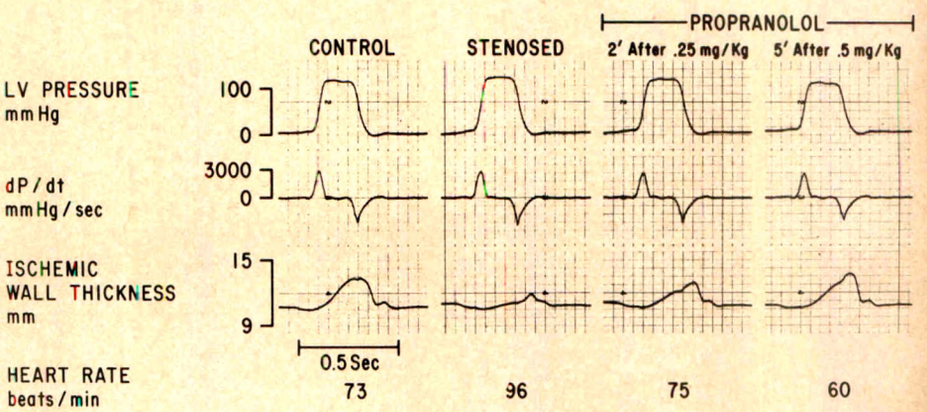


FIGURE 5. Effects of partial coronary constriction followed by administration of propranolol in the conscious dog on left ventricular (LV) pressure and its first derivative (dP/dt), ischemic wall thickness dynamics and average heart rate. Severely depressed active wall thickening in the ischemic area after coronary narrowing was induced recovers as heart rate decreases after propranolol. Note that wall thickening patterns are reciprocal to those in the tracings of segment shortening in the ischemic zone (Fig. 2).

I). Average dP/dt decreased slightly but not significantly, and tension-time index tended to decrease after propranolol but the change was not statistically significant (Table I).

Regional myocardial function: In the ischemic segment, end-diastolic length tended to increase after administration of propranolol but the average change was not significant. Percent shortening of the ischemic segment improved progressively (Fig. 1) and reached 11.8 percent (P <0.01) 5 minutes after propranolol (Table I, Fig. 4). With improvement of ischemic segment shortening after propranolol, regional stroke work and minute work were increased significantly to a level near that observed during the control state (Table I).

In the control area, end-diastolic segment length was unchanged; percent segment shortening and regional stroke work after propranolol tended to be reduced, but the changes were not significant (Table I). However, minute work of the control segment was reduced significantly by 30 percent (Table I), and maximal shortening velocity also decreased (Table I). The changes in regional segment function are correlated with changes in flow ratio after propranolol in Figure 3.

Pacing after propranolol: Hemodynamic changes produced by atrial pacing at the same rate as that existing during coronary stenosis before the administration of propranolol (95/min) were not significant. End-diastolic segment lengths decreased slightly with pacing in both control (0.17 ± 0.14 mm [P <0.02]) and ischemic (0.13 ± 0.12 mm [P <0.05]) segments. Percent shortening of the control segment, which decreased slightly but not significantly after administration of propranolol, showed no further change during pacing (Fig. 4). Ischemic segment percent shortening decreased (P <0.01) during pacing after propranolol but remained improved compared with values in the stenosed state before administration of propranolol (Fig. 4).

Wall Thickness Measurements

With coronary stenosis, percent wall thickening in the ischemic area was reduced significantly (Fig. 5) without significant change in end-diastolic thickness (Table III). Five minutes after the administration of propranolol, percent thickening in the ischemic area recovered from an average of 0.9 to 13.4 percent. Wall thickening of the control area tended to decrease after propranolol, but the change was not significant.

After release of the stenosis, reactive hyperemia occurred, and by 10 minutes the flow pattern was normal with mild residual depression of ischemic segment shortening (Fig. 1 and 3).

Discussion

After coronary occlusion, holosystolic elongation (bulging) in ischemic zones was observed with a variety of techniques,[3–5,10,11,13–18] in open chest and conscious animals, and sustained hypokinesia was observed in adjacent marginal regions.[3,4] Lessening of dysfunction in such marginal areas was observed after the administration of propranolol, nitroglycerin and morphine.[3,4] Hypofunction was previously observed during acute coronary underperfusion in open chest dogs[19,20] and in the chronic state after myocardial infarction in which the marginal segment was composed of a mixture of normal and scar tissue.[5] The wave forms of regional contraction in the hypoperfused ischemic segments in our study appear to be closely similar to those occurring in marginal segments after acute coronary occlusion.[3,4] However, analysis of marginal segments of myocardium adjacent to a nonfunctional segment produced by total occlusion of a coronary artery may not provide a valid model for the study of partial coronary narrowing because mechanical tethering of the partially perfused area by the nonperfused area might influence the observed pattern of shortening.[21] In addition, if a precise spatial demarcation existed between fully normal and nonfunctional myocardium during total coronary occlusion, and if the crystals were placed across this border, the effects of drugs on the wave form of this segment might be due primarily to effects on the function of the normal tissue between the measuring crystals.

For these reasons, we developed a preparation that should overcome these limitations and be closer to the clinical setting in angina pectoris by limiting regional coronary blood flow to produce stable regional hypofunction in the ischemic area. Recently this model was also applied to the study of regional dysfunction produced by strenuous exercise in dogs with stenosis-lim-

ited coronary reserve when coronary flow was sufficient to maintain relatively normal regional myocardial function at rest.[22]

Partial versus complete coronary arterial occlusion: The effects of partial narrowing of the circumflex coronary artery on the behavior of the dogs and on hemodynamic measures and regional function were less severe than those previously reported[4] to occur after complete occlusion of this artery in the conscious dog. With partial coronary stenosis some dogs appeared restless, but we never observed the severe agitation frequently seen after coronary occlusion without sedation.[4] Regional myocardial function tended to be more labile during partial coronary constriction than with complete occlusion; for example, when the animal stretched its limbs or was excited by laboratory noise, heart rate increased and ischemic segment shortening sometimes became further depressed, requiring elimination of the data from that experiment. Ventricular arrhythmias were very rare in our study, whereas they are common in complete coronary occlusion.[4] Average heart rates increased by 17 beats/min above control rate, an increase less than that after complete occlusion (37 beats/min).[4] Peak left ventricular systolic pressure, end-diastolic pressure and peak dP/dt showed almost the same pattern after partial coronary stenosis as with complete coronary occlusion, but changes were less marked.[4]

Favorable effects of propranolol on myocardial function in ischemic area: A highly favorable action of propranolol on myocardial contraction in the ischemic area was noted, suggesting that propranolol caused amelioration of the regional imbalance between oxygen supply and demand. One effect of the drug was a reduction to below control level of the elevated heart rate that accompanied partial coronary arterial constriction; heart rate is well known to be a major determinant of myocardial oxygen consumption.[23–25] Other factors relating primarily to coronary blood flow and its distribution may have been operative.

The increase in diastolic time after heart rate reduction has a favorable effect on subendocardial perfusion,[26,27] and reduction of heart rate has been reported to decrease the vascular resistance of the endocardium in chronic experimental coronary occlusion.[28] In addition, early diastolic flow velocity was increased in our study (Fig. 2). It is also possible that, once myocardial contraction began to recover after propranolol, wall stress in the subendocardial ischemic zone was reduced,[29] further favoring a sustained increase in coronary flow. In support of this possibility is one preliminary observation[30] that in some dogs mean coronary blood flow through a narrowed artery actually decreases when severe regional dyskinesia develops during rapid cardiac pacing; also O'Riordan et al.[31] showed that subendocardial flow tended to decrease during rapid pacing in the presence of coronary stenosis, and in some dogs total flow decreased. In our experiments the absence of a significant difference between mean coronary blood flow and the control value after propranolol, despite the presence of coronary stenosis, may be partly explained by this mechanism. In addition, the stenosis was adjusted and fixed while the reflex increase in heart rate was developing; thus, regional ischemia may have been more exaggerated than would have been the case had the tachycardia not occurred and if the stenosis could have been fixed at the control heart rate.

Whether the dyskinetic response of myocardial function to acute coronary stenosis that we observed is similar to the type of acute deterioration in ventricular function that can occur during anginal episodes unassociated with exercise is uncertain. However, the beneficial effects of propranolol that we recorded appear to provide additional insight into mechanisms that may be operative under such conditions of acute ischemia.

When the heart rate was matched by atrial pacing after propranolol with the rate existing before administration of the drug, ischemic segment function, although reduced, remained improved. This finding suggests an additional possible effect of propranolol, such as coronary blood flow redistribution between uninvolved and ischemic areas, perhaps by way of collateral channels.[32,33] The control segments tended to show end-diastolic elongation and reduced shortening velocity after propranolol, thus suggesting depressed myocardial function; there was also a 30 percent reduction of regional work after propranolol, which should have reduced myocardial oxygen consumption in the normal regions even though the reduction in tension-time index (reflecting total cardiac oxygen consumption[23]) was not statistically significant. Decreased inotropic state and velocity of shortening may also have diminished oxygen consumption.[24,25] Therefore, the net effect of propranolol may have been diminution of the discrepancy in oxygen demand between the control and the ischemic areas,[4,32,34] which could have lessened any "steal" phenomenon existing after partial coronary stenosis[35] before the administration of propranolol.

Changes in coronary flow pattern accompanying coronary stenosis and hypokinesia: The reduction of regional shortening in the ischemic area accompanying coronary stenosis was associated with a change in the coronary blood flow pattern, an elevated systolic/diastolic pattern usually being observed. Gregg and Fisher[36] described a similar pattern in the hypotensive dog without coronary stenosis, and recently Sanders et al.[37] also reported preliminary observations of such a phenomenon in the pig during partial coronary stenosis using an electromagnetic flowmeter on the coronary artery. The exact mechanism of these changes in the coronary blood flow pattern is not known, but the following sequence of events provides a plausible explanation: (1) Regional systolic resistance in the coronary vascular bed (due to the mechanical effect of local cardiac contraction) decreases significantly after coronary stenosis because of hypokinesia, and the mean and diastolic coronary vascular resistance levels are reduced as the coronary bed dilates in response to the imbalance between oxygen supply and demand.[38,39] (2) Because the coronary arterial pressure distal to a stenosis follows the systemic arterial pressure wave form,[34] the weak myocardial contraction coupled with low vascular re-

sistance allows greater coronary flow in systole than in diastole. This effect may be likened to the situation in the right coronary artery,[40] in which the right ventricular intramyocardial pressure is not sufficiently high to inhibit an increase in systolic coronary blood flow consequent to the high systolic aortic perfusion pressure. There is evidence that systolic coronary blood flow in the intact left ventricle preferentially nourishes the epicardium, whereas subendocardial perfusion may be mainly provided during diastole.[26,27] Whether the prominent systolic coronary flow that we observed during coronary arterial narrowing provides blood primarily to the epicardium, or to the ischemic subendocardium also, remains to be established by experiments with radioactive microspheres.

Interpretation of results: From these considerations, it is apparent that interpretation of the responses observed will require further study. It seems likely that the dominant effect produced by propranolol was a reduction in myocardial oxygen requirements effected by slowing, to a rate below control level, the moderate tachycardia that invariably accompanied coronary constriction and may be reflex in origin.[4] However, the pacing studies, other experimental work and the dramatic nature of the improvement in regional function and flow pattern indicate that other factors probably were also operative.

We cannot entirely exclude the possibility that some change in position or inflation of the fluid-filled cuff during partial coronary stenosis that favored increased coronary flow might have occurred after administration of propranolol. However, other manipulations (such as pacing and exercise) of this same preparation over longer time intervals have not resulted in change of the stenosis as indicated by regional function. Additionally, changes in systolic arterial pressure after propranolol were small or absent, and the longer diastolic period due to reduced heart rate should have led to a decreased rather than an increased aortic diastolic pressure and perfusion gradient. In addition, in these chronically instrumented animals, firm adhesions take place and a consistent movement of the cuff seems most unlikely to have occurred.

Average percent shortening of the segments in the inferolateral region of the heart to be rendered ischemic was less than that of anterior segments under control conditions. There was no evidence at postmortem examination of circumflex coronary arterial narrowing or myocardial infarction in its distribution; it is possible that the reduction in shortening may relate to differences in regional shortening that exist in the normal left ventricle.[41]

Wall thickness measurements showed responses directionally similar to those observed for regional segment length during ischemia and treatment with propranolol. This observation further supports the application of wall thickness measurements to assessment of acute changes in regional myocardial function[11] and their potential value in the clinical setting by means of echocardiography.[10]

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Recording From the Body Surface of Arrhythmogenic Ventricular Activity During the S-T Segment

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Recent experimental reports have documented the delay of epicardial potentials beyond the QRS complex as a result of infarction, and the degree of delay was directly associated with the onset of ventricular arrhythmias. This study describes a method using high amplification, band pass filtering and signal averaging for recording from the body surface these delayed potentials presaging ventricular arrhythmias. This technique has been used for recording low level cardiac potentials masked by noise. In 10 dogs control records of the electrocardiogram and surface averaged lead were obtained during sinus rhythm, atrial pacing and premature atrial beats. Subsequently, the left anterior descending coronary artery was ligated in each dog. Nine dogs survived the surgical procedure and underwent similar recordings 3 to 6 days after infarction. Electrocardiographic changes were consistent with a recent infarction. During the pacing protocol discrete multiphasic wave forms appeared during the S-T segment of the surface averaged lead, and concomitant changes in the terminal portions of the QRS complex were observed in seven dogs. In five of these dogs ventricular arrhythmias were observed at the faster pacing rates or after closely coupled premature atrial beats. The chest was then reopened and the pacing procedure repeated during recording of direct epicardial electrograms with a multicontact bipolar electrode. This electrogram validated the existence of potentials during the S-T segment in all but one dog and late activity that was not repeatable on a beat to beat basis in another. Thus, when late activity was confirmed with the epicardial electrogram, seven of eight dogs showed a corresponding change in the surface averaged lead. This technique may prove to be a sensitive indicator of abnormal electrical activity preceding ventricular arrhythmias.

Although the concept of reentrant arrhythmias has existed for some time, little direct evidence of this mechanism has been reported. In 1973 Boineau and Cox[1] showed that electrograms from ischemic regions of the canine heart were delayed and fractionated. Scherlag,[2] Hope[3] and Williams[4] and their co-workers quantified the relation between this delayed ventricular activation and ventricular arrhythmias. Waldo and Kaiser[5] also described the bridging of the diastolic interval with electrical activity preceding arrhythmia. More recently, El-Sherif [6,7] and Hope[8] and their co-workers demonstrated a consistent model for observing this continuous electrical activity during premature atrial contractions and alterations of heart rate. These observations provided persuasive evidence for the existence of reentrant pathways.

None of these studies showed alterations of the QRS complex of the sinus beats preceding the reentrant ventricular beat attributed to the timing and sequence of activation of the ischemic epicardium. It is likely that the areas showing marked delay have a small total mass compared with the entire ventricular mass, and therefore their activation is not

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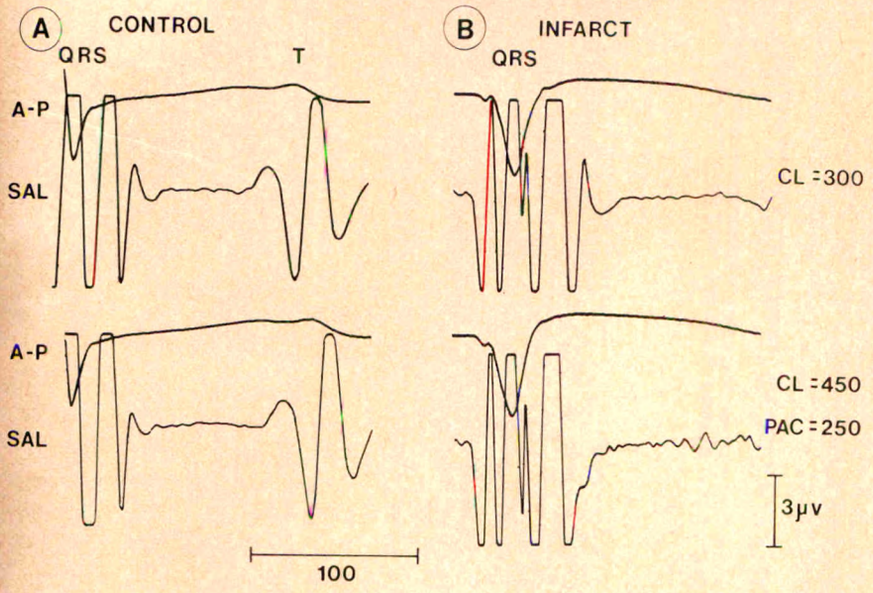


FIGURE 1. Recordings of the anterior-posterior (A-P) electrocardiogram and the surface averaged lead (SAL) before **(A)** and 3 days after coronary arterial ligation **(B)**. The upper section of each panel was obtained at a paced heart rate with a cycle length (CL) of 300 msec. The lower section of each panel was obtained with a paced heart rate (cycle length 450 msec) and the introduction of a premature atrial complex (PAC) every third cycle at a coupling interval of 250 msec. The 3 μv vertical scale applies only to the surface averaged lead, and the horizontal scale represents 100 msec. In this and succeeding figures all unqualified numbers represent milliseconds.

detected with the electrocardiogram. The technique of signal averaging[9] aids in the recording of low level potentials. Previous work in our laboratory utilized this technique to record His-Purkinje potentials from the body surface in dogs[10] and man,[11] and from the boundaries of the isolated tissue bath,[12] as well as to record atrioventricular nodal potentials from electrode catheters.[13] By combining the experimental model showing delayed ventricular potentials associated with ventricular arrhythmias and the signal averaging technique, we recorded from the body surface potentials that correlate in time with this late ventricular activation. These potentials are in the microvolt range and would not be expected to be recorded in the standard electrocardiogram.

Methods

Experimental procedure and pacing protocol: Ten mongrel dogs weighing 12 to 20 kg were anesthetized with sodium pentobarbital, 30 mg/kg body weight. The dogs were placed on a mechanical respirator, and electrocardiographic leads were attached for monitoring on an oscilloscopic photographic recorder (Electronics for Medicine DR-12). A bipolar lead was placed across the chest in an anterior-posterior axis at the level of the fourth intercostal space. This lead was used to record the surface averaged lead to be described. A bipolar pacing catheter was inserted into the right atrium through the external jugular vein. Control records of electrocardiographic leads II, III, aVR and the surface averaged lead were obtained (1) during sinus rhythm; (2) during atrial pacing at cycle lengths of 450, 400, 350 and 300 msec; and (3) at cycle lengths of 450 msec and 400 msec with premature atrial complexes introduced every third cycle at coupling intervals of 300, 250 and 200 msec. The pacing system utilized the Tektronics 2600 series pulse and ramp generators and a special module described by Wagoner et al.[14]

After control records were obtained, the left side of the chest was opened under sterile conditions at the fourth intercostal space. The pericardium was incised and reflected to expose the left anterior descending coronary artery. The artery was ligated midway along its length and the chest closed. The animal was returned to the kennel and treated with antibiotic agents. Three to 6 days postoperatively the animal was reanesthetized. The same electrocardiographic and surface averaged lead recordings were obtained with the pacing protocol used in the control period. At this time, three dogs also underwent another pacing protocol previously described by Hope et al.[8] This protocol involves turning the pacer off and on repeatedly and, because of the long-short cycle sequences, is an arrhythmia-provoking procedure. The chest was reopened through the initial incision and the heart again exposed. A large surface, multicontact bipolar electrode was placed on the apex area to record epicardial potentials from the infarct zone as well as from the adjacent normal zone. The details of this electrode have been described previously.[3,4,6–8] The same pacing protocol was repeated while the electrocardiographic leads and epicardial electrograms were recorded.

Signal averaging system: The bipolar anterior-posterior lead was differentially amplified (Princeton Applied Research 113) with a gain of 1,000. This signal served as the electrocardiographic lead for the signal averaging recordings and was further processed to become the surface averaged lead. The second stage of processing was band pass filtering between 60 and 300 hertz (Krohn-Hite 3750). The signal was further amplified (Analog Devices 171) by a factor of 750. The electrocardiographic signal and surface averaged lead were directed to the input of the signal averager (Hewlett-Packard 5480B).

Signal averaging will improve the signal to noise ratio of repeatable or triggerable events such as the electrocardiogram by the square root of the number of cycles averaged.[9] The specific methods were described in detail in previous work from our laboratory[10–12]; therefore only the different aspects of the technique will be described here. A 200 msec window of the cardiac cycle that included the QRS complex, S-T segment and a portion of the T wave was analyzed. During sinus rhythm a QRS detector was used to trigger the averager; during the pacing protocols the output from the pacer was used. When a premature atrial complex was introduced only that complex was averaged because it was possible to trigger the averager with the premature pulse by means of an auxil-

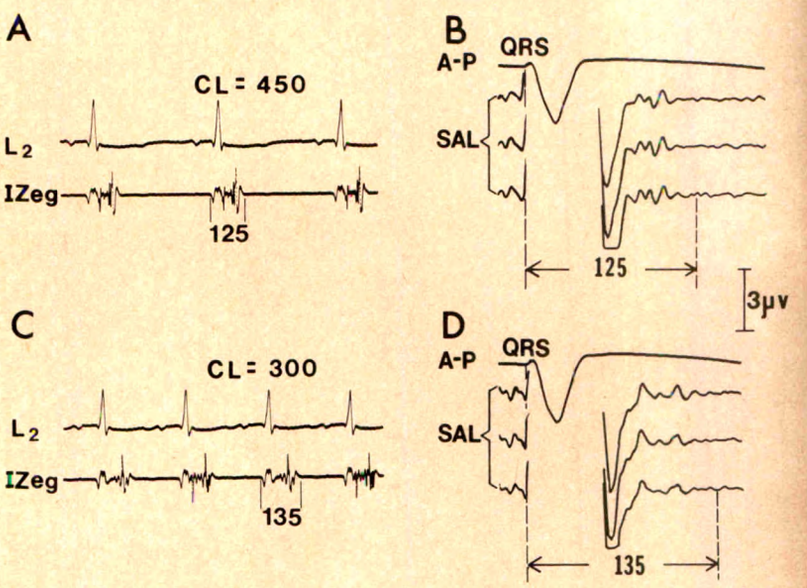


FIGURE 2. Comparison of the electrogram from the infarct zone (IZeg) and three serially obtained surface averaged leads (SAL) at two different atrial pacing rates. Panels **A** and **B** were obtained at a cycle length of 450 msec and panels **C** and **D** at a cycle length of 300 msec. The duration of ventricular activity in the infarct zone electrogram is 125 msec in panel **A** and 135 msec in panel **C**. These durations were translated to panels **B** and **D**, respectively. The **vertical** scale applies to the surface averaged lead only. Abbreviations as in Figure 1.

iary output of the stimulator. The temporal stability of the trigger within the cardiac cycle was within ±2 msec. Each of the signal-averaged records shown in this study was obtained over 64 cardiac cycles. The system allowed the repetition of up to three separate averages so that each surface averaged lead could be compared for reproducibility between sets of averages.

Results

Control period: The focus of this study was on the S-T segment because previous animal studies demonstrated delayed epicardial potentials during this period. In none of the control studies was there evidence of delayed potentials or of alteration in the terminal portion of the highly amplified and filtered QRS complex as a function of the pacing protocol.

Figure 1A is a typical example. The lower half of panel A was obtained by averaging only the S-T segment of the premature atrial complexes. The surface averaged lead had 750 times the amplification of the anterior-posterior lead, and band pass filtering ranged from 60 to 300 hertz. The control recordings of the surface averaged lead showed no appreciable change during the S-T segment, and the terminal portion of the QRS complex was not altered. However, the duration of the Q-T interval changed in relation to heart rate.

After coronary arterial ligation: *Figure 1B* was obtained 3 days after ligation and the upper and lower portions were obtained using the same pacing rate as in Figure 1A (cycle length 300 msec). The S-T segment of the anterior-posterior lead was changed from the control state. In the surface averaged lead, the terminal portion of the QRS complex has changed in configuration and the S-T segment contains a multiphasic wave form. This wave form was reproducible, and at the 250 msec coupling interval premature complexes were seen.

Degree of reproducibility and correlation with the recording of delayed epicardial potentials: These are shown in Figures 2 and 3. All of the data in these two figures were obtained from the same dog 3 days after infarction.

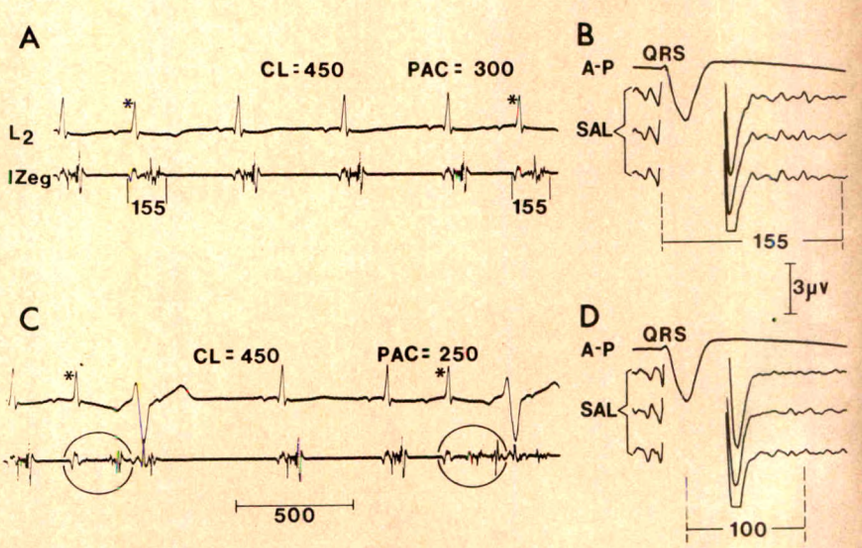


FIGURE 3. Comparison of the electrogram from the infarct zone (IZeg) and three serially obtained surface averaged lead (SAL) recordings at the same cycle length (CL) but at two different coupling intervals of the premature atrial complexes (PAC). In **A** and **B** the coupling interval is 300 msec. The premature atrial complex in lead II (L_2) is marked by an **asterisk**. Only the premature atrial complexes were averaged to constitute the surface averaged lead. The duration of ventricular activity measured in the infarct zone electrogram of panel **A** was 155 msec. This time was transferred to panel **B** for comparison. The coupling interval of the premature atrial complex in panel **C** was 250 msec. Each premature atrial complex was followed by a reentrant ventricular beat. The activity of the infarct zone electrogram is of low level and continuous at this time **(encircled)**. The 100 msec scale in panel **D** is for reference. A-P = anterior-posterior.

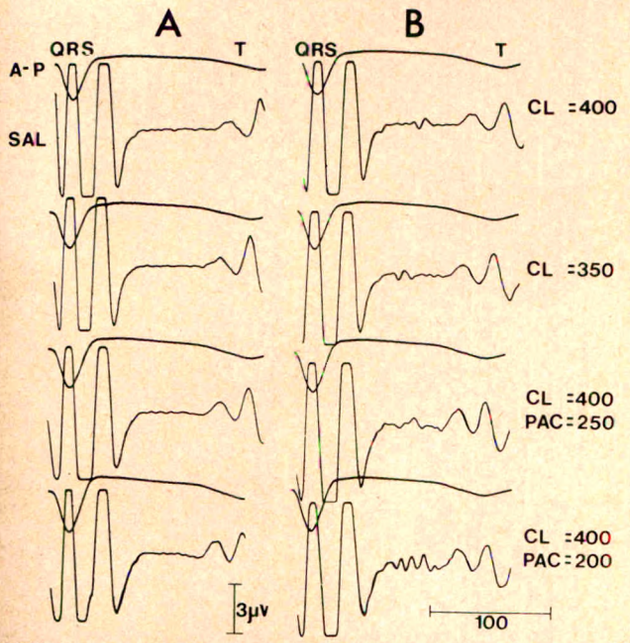


FIGURE 4. Comparison of the anterior-posterior (A-P) lead and surface averaged lead (SAL) before **(A)** and after **(B)** the appearance of arrhythmias in a dog 4 days after coronary arterial ligation. The cycle length (CL) and premature atrial complex (PAC) coupling interval of each section of **A** and **B** are indicated **at right**. The **vertical scale** applies only to the surface averaged lead.

Figure 2, A and B was obtained during atrial pacing at a cycle length of 450 msec. Panel B was obtained before the chest was reopened to record epicardial potentials from the infarct zone. Each surface averaged lead tracing in panel B has a reproducible wave form after the apparent normal termination of ventricular activity. The infarct zone electrogram of panel A shows a reproducible recording of 125 msec duration from the onset of the QRS complex. This duration is transposed to panel B. The reproducible portion of the late ventricular activity seems to end before this marker. Similar data are seen in panels C and D, both obtained with a cycle length of 300 msec. In this case the epicardial potential is 135 msec in duration. The reproducible portion of the surface averaged lead ends before this time, but this activity has increased in duration by about 13 msec over that in panel B.

Figure 3, presented in the same format as Figure 2, was obtained during the induction of premature atrial complexes. Panels B and D are averages of only the premature cardiac cycle. Panels A and B were obtained with a cycle length of 450 msec and a coupling interval of 300 msec; panels C and D had the same basic cycle length but the extra complex coupling interval was 250 msec. In panel A the duration of the electrogram of the infarct zone was 155 msec and was reproducible in each set of 64 averages taken. Panel B is marked with a time interval of 155 msec, and it appears to exceed the reproducible portions of the late occurring ventricular potentials. Compared with Figure 2D, there is an increase of about 16 msec in the duration of these reproducible potentials.

The coupling interval was 250 msec in panels C and D, and reentrant ventricular complexes are evident after every premature atrial complex. The infarct zone electrogram showed late occurring potentials (circled area) preceding the ventricular complex, but the activity was not reproducible even though the QRS deflections of the ventricular complexes were identical. This lack of consistency during the S-T segment may account for absence of reproducible potentials in the surface averaged lead in panel D.

Surface averaged lead before and after occurrence of reentrant beats: In three dogs studied after infarction no changes were seen in the surface averaged lead during the usual pacing protocol. In one dog, the epicardial electrode also showed no late activity; in another, late activity did appear in the epicardial electrogram. In the third dog another pacing protocol[8] was used before the chest was opened; because reentrant ventricular arrhythmias were seen, the original pacing protocol was repeated.

The results are shown in Figure 4. Panel A depicts the data before the occurrence of reentrant beats; in each surface averaged lead there is no change in the terminal portion of ventricular activity and no distinct wave forms appear in the S-T segment. Panel B depicts the data after the occurrence of reentrant beats; the surface averaged lead of each section shows a distinct wave form in the S-T segment. The most complex wave form is in the lowest section where the cycle length was 400 msec and the coupling interval of the premature atrial complex was 200 msec. At this time reentrant ventricular beats similar to those in Figure 3 were seen. In all eight sections of Figure 4 the anterior-posterior lead of the electrocardiogram showed no evidence of change in configuration of either the QRS complex or the S-T segment. Although only one surface averaged lead is shown for each pacing procedure, three separate averages of 64 cycles were obtained and reproducibility of each surface averaged lead was observed.

Thus, the absence of arrhythmias at one time during the study was associated with absence of late activity in the surface averaged lead, whereas the appearance of arrhythmias in eight cases corresponded with detection of late activation in the S-T segment recorded at the body surface.

Discussion

Late S-T segment potential activity during myocardial infarction: The ability of the signal averaging technique to record low level potentials has been well established.[9–13] The deflections observed during the S-T segment of the surface averaged lead are in the microvolt range, which is also within the range of resolution of the technique. Without band pass filtering, the normal low frequency content of the S-T segment and that due to changes associated with infarction do not allow high levels of gain to be used. An optimal band width was not determined in this study. The band width may be an important variable for devising a more quantitative measure of the S-T segment for future studies. It is possible that the observed potentials reflect changes in configuration of the S-T segment; that is, they may be repolarization or injury potentials resulting from ischemia. The data in Figures 2 and 3 show that the presence of these potentials is related to heart rate; however, the S-T segments in the electrocardiogram of both the strip recordings and the averaged anterior-posterior leads did not show any configurational changes with heart rate. Furthermore, these deflections were associated with arrhythmias. The dog with infarction but without arrhythmias (Fig. 4A) had no S-T changes associated with the standard pacing protocol in either the anterior-posterior or the surface averaged lead. After another pacing protocol[8] that induced ven-

tricular arrhythmias, the S-T segment of the surface averaged lead showed marked changes (Fig. 4B). Thus, rate-dependent and arrhythmia-correlated deflections were observed in the S-T segment of the surface averaged lead that were not evident in the standard electrocardiogram. Finally, the duration of the deflections in the surface averaged leads corresponded with delayed epicardial activity recorded directly from the infarcted epicardium.

In two dogs arrhythmias were not observed as a result of pacing, and the S-T segment of the surface averaged lead remained unchanged. The epicardial electrogram of one of these dogs did not show late occurring potentials. This dog was studied 6 days after infarction, and it is possible that healing had progressed so that delayed activation and arrhythmias did not occur in response to the pacing protocol. In the other dog delayed activity was detected with the epicardial electrogram, but it was not consistent on a beat to beat basis. This dog reflects the Wenckebach-like, ischemic zone activity seen over a wide range of heart rates described by El-Sherif et al.[6,7] The signal averaging technique would not be expected to register this activity in any reproducible fashion because it changes from beat to beat. Another example of this nonrepeating activity is seen in Figure 3D. In this case the nonrepeating nature of the late epicardial activity was a function of the coupling interval. Even though delayed activity preceded each reentrant ventricular beat of Figure 3C, it was variable. Consequently, the averages in Figure 3D are of low level and not reproducible.

These three dogs that had no reproducible potentials within the S-T segment provide an additional control for the data. Thus, it is not possible to ascribe the changes in the S-T segment to surgery or anesthesia alone or in combination. The case in which the pacing protocol of Hope et al.[8] provoked both the appearance of arrhythmias and the concomitant changes in the S-T segment also negates the possibility that the latter changes are nonspecific effects of surgery or anesthesia.

Methodologic considerations in measurement of ventricular activity: Because each point of the surface averaged lead is the result of a 64 cycle average, it is possible to obtain other statistical measures such as the variance or standard error. To evaluate periods of nonrepeatable activity with signal averaging, it may be helpful to calculate the variance. This measurement may be more sensitive to changes within the S-T segment at these times because of the probable wider spread of the data above and below the average. A programmable computer with appropriate interfacing and programs can calculate the variance and has been used in the study of averaged evoked responses.[15]

The duration of ventricular activity measured in Figures 2, A and C, and 3A was transferred to the corresponding signal-averaged record of Figures 2, B and D, and 3B for comparative purposes. In no case was an exact correlation found because the end of ventricular activity in the surface averaged lead was indeterminate. Many factors may account for this finding, such as the use of only one surface averaged lead, suboptimal filter band width, inadequate gain or an insufficient number of averaged cycles.

The measurements of ventricular activity in the infarct zone electrogram of Figures 2, A and C, and 3A were 125, 135 and 155 msec, respectively; these corresponded to measurements of ventricular activity in the surface averaged lead of Figures 2, B and D, and 3B of 110, 130 and 140 msec, respectively. These data have a correlation coefficient of 0.93, but the data set is too small to permit reliance on this statistical measurement. This experiment was the only one in which a correlation occurred. Generally, the late occurring activity in the surface averaged lead overlapped the early part of the T wave (Fig. 4), or the averaging window was not appropriately sized (Fig. 1) to allow such measurements. The latter is the result of the hard-wired averager in which the choice of sweep speed was limited. Future studies should include an increased averaging window with appropriate resolution because late epicardial activity does occur up to the onset of the reentrant beat. Thus, the T wave and the diastolic interval should also be examined.

Implications: This preliminary study has shown that the S-T segment of the precordial electrocardiogram contains more information than previously suspected. This activity is the result of ischemia and is associated with the onset of ventricular arrhythmia. Previous animal studies utilizing the multicontact bipolar epicardial electrode adequately documented the reentrant nature of this activity. Our study demonstrates that signal averaging can detect this activity from the body surface. The extension of similar signal averaging techniques to man may become a noninvasive diagnostic method of measuring the prodrome of ventricular arrhythmias.

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Electrophysiologic Properties of a New Antiarrhythmic Drug—Tocainide

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Tocainide (Astra W36095) is an orally active antiarrhythmic drug that is structurally related to lidocaine. This paper describes in vivo and in vitro studies undertaken to assay the electrophysiologic properties of this compound. Ouabain-induced ventricular ectopic activity was abolished by this drug in both isolated canine Purkinje fibers and in intact dogs. Similarly, the ventricular ectopic activity that occurs 24 hours after the two stage Harris coronary arterial ligation procedure also was abolished by tocainide. The amount of current necessary to evoke an action potential by intracell stimulation during diastole was increased in direct relation to drug concentration. Similarly, in dogs anesthetized with pentobarbital sodium, tocainide increased the ventricular fibrillation threshold up to 150 percent above control values during normal supraventricular rhythm and up to 285 percent after premature ventricular beats. The transmembrane action potential duration and effective refractory period of isolated canine Purkinje fibers were shortened by tocainide. Tocainide depressed atrioventricular nodal conduction in anesthetized dogs, an effect that was magnified in the presence of premature atrial beats but had no effect on His, Purkinje or ventricular muscle conduction. These results indicate that tocainide is a potentially effective antiarrhythmic agent and deserves further investigation in patients.

Currently available drugs used to prevent lethal cardiac arrhythmias either have undesirable side effects or can be administered only parenterally. Encouraging preliminary clinical studies[1–3] of a new oral drug, tocainide (Astra W36095), have shown that it has definite antiarrhythmic activity, minimal side effects and a long therapeutic half-life. These experiments were designed to measure electrophysiologic effects of tocainide that provide information about its mechanism of antiarrhythmic action and toxic effects.

Methods

In vivo preparations: Experiments were performed using 24 mongrel dogs of either sex anesthetized intravenously with either pentobarbital sodium (30 mg/kg body weight, or alpha chloralose (80 mg/kg). The heart was exposed with either a right thoracotomy or a median sternotomy and the animals were ventilated with room air using a positive pressure ventilator. Electrograms obtained with close bipolar stainless steel plunge electrodes from the atria, bundle of His and ventricles were recorded simultaneously with a lead II electrocardiogram.

Electrodes were also applied to the right atrium to pace the heart at a constant basic cycle length and to induce premature atrial depolarizations. These methods have been fully described previously.[4] Data were recorded on 35 mm film and analyzed with a programmable calculator and digitizer. Time intervals could be accurately measured within ±2 msec. Tocainide was usually administered intravenously as a 2 percent concentration in normal saline solution at rates of 0.5 to 2 mg/kg per min. In several experiments, tocainide was administered as a bolus injection. Tocainide plasma concentrations were determined in venous blood samples with a chromatographic method previously described.[3]

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TABLE I

Effects of Tocainide on Ventricular Arrhythmias in Four Dogs With Ouabain Toxicity

		Control Period			At Maximal Effect			
Dog (no.)	Ouabain Dose (mg/kg)	Ventricular Heart Rate (beats/min)	Mean Arterial Pressure (mm Hg)	Percent Ectopic Beats	Ventricular Heart Rate (beats/min)	Mean Arterial Pressure (mm Hg)	Percent Ectopic Beats	Plasma Tocainide Concentration (μg/ml)
1	90	204	115	100	135	130	0	22.7
2	70	213	140	100	129	145	0	20.6
3	70	225	170	98	186	175	0	—
4	90	171	110	100	120	105	0	11.7
Mean	80.0	203	133.7	99.5	142	138.7		18.3
± SD	± 11.5	± 23.2	± 27.5	± 1.0	± 29.6*	± 29.3		± 5.8

*Significantly different from control value (probability [*P*] = 0.01).
SD = standard deviation.

In the ventricular fibrillation threshold experiments, bipolar electrodes, 1 mm in diameter and 5 mm apart, were sutured to the epicardial surface of the right ventricle. The ventricular fibrillation threshold was measured as the minimal current in milliamperes that could induce fibrillation when a constant current 100 hertz train of 120 msec duration was applied during the vulnerable period. This technique has been fully described previously.[6]

Ventricular tachycardia was produced with either digitalis cardiotoxicity or the Harris two stage left anterior descending coronary arterial occlusion technique.[7] In the digitalis toxicity experiments, ouabain was infused intravenously at a loading dose of 40 μg/kg and followed 30 minutes later by an additional dose of 20 μg/kg. Subsequently, at 30 minute intervals 10 μg/kg was administered until ventricular tachycardia developed in which greater than 85 percent of the ventricular complexes were of ventricular origin. Tocainide was then infused intravenously until the ectopic ventricular activity was suppressed. The electrocardiogram was monitored for 90 minutes after the initiation of tocainide infusion. In the two stage Harris occlusion studies, a ventricular tachycardia was studied 24 hours after experimental coronary occlusion. Tocainide was infused at a rate of 0.5 mg/kg per min until 100 percent suppression of the ventricular rhythm occurred.

In vitro preparations: Hearts were removed from 18 dogs of either sex anesthetized with sodium pentobarbital (30 mg/kg administered intravenously), and Purkinje fiber–papillary muscle preparations from the right and left ventricles were excised and maintained in oxygenated temperature-regulated Tyrode solution (2.7 millimolar potassium). Standard microelectrode techniques were employed to record transmembrane potentials from the Purkinje fiber cells. The fibers were paced through bipolar Teflon®-coated silver surface electrodes. Pacing was accomplished with a 1 msec constant current pulse that was twice diastolic threshold for the normal drive stimuli and three times diastolic threshold for determination of the effective refractory period. The rates of membrane depolarization were derived electronically, and all data were recorded on 35 mm film. Intracell stimulation and recording with a single microelectrode was employed to measure excitability in single Purkinje fibers.[8]

In the in vitro tissue experiments, tocainide was added directly to the tissue bath to attain predetermined concentrations. The concentrations of tocainide were subsequently confirmed in aliquot samples. At least 5 minutes was allowed at each level of tocainide for equilibration before intracell measurements were made.

Results

In Vivo Experiments

Ventricular tachycardia: Tocainide abolished 100 percent of ventricular ectopic complexes induced by ouabain in four anesthetized dogs at tocainide plasma levels of greater than 11.7 μg/ml (Table I). The average plasma level of to-

TABLE II

Effects of Tocainide on Ventricular Arrhythmias in 10 Dogs 24 Hours After Acute Coronary Occlusion

	Control Period			At Maximal Effect			
Dog no.	Ventricular Heart Rate (beats/min)	Mean Arterial Pressure (mm Hg)	Percent Ectopic Beats	Ventricular Heart Rate (beats/min)	Mean Arterial Pressure (mm Hg)	Percent Ectopic Beats	Plasma Tocainide Concentration (μg/ml)
1	210	65	87	141	95	5	30.6
2	213	85	95	174	140	0	30.5
3	207	105	91	162	110	4	27.4
4	204	125	99	147	130	6	49.7
5	192	115	94	132	110	0	67.0
6	198	115	94	153	190	0	48.5
7	177	105	90	141	115	3	23.8
8	240	110	93	165	135	3	67.5
9	216	105	92	156	115	6	40.1
10	195	100	100	129	135	0	—
Mean	205.2	103	93.5	150.5	127.5	2.7	42.8
± SD	± 16.8	± 17.0	± 3.9	± 14.0*	± 26.2	± 2.5*	± 16.5

*Significantly different from control value ($P < 0.001$).

cainide required to achieve complete suppression was 18.3 μg/ml. There was no significant change noted from control in P/R interval or QRS duration after the return to sinus rhythm.

In the 10 dog preparations studied with coronary occlusion produced by the Harris method, tocainide suppressed 50 percent of ventricular ectopic complexes at an average blood level of 18.7 ± 2.3 μg/ml; for 100 percent suppression, plasma levels of 42.8 ± 16.5 μg/ml were required (Table II). In this model 87 to 100 percent of the QRS complexes were of ectopic ventricular origin 24 hours after coronary ligation. The plasma tocainide level required for 100 percent suppression at this time ranged from 23.8 to 67.5 μg/ml.

In both the digitalis toxicity and coronary ligation experiments, the termination of tocainide infusion was always accompanied by resumption of ventricular tachycardia. Ninety minutes after the termination of infusion, the ventricular ectopic frequency was more than 75 percent of the control value.

Ventricular fibrillation threshold: Tocainide increased the ventricular fibrillation threshold during both normal sinus rhythm and programmed premature ventricular depolarizations. In Figure 1 a consistent dose-related increase in ventricular fibrillation threshold determined during normal sinus rhythm is apparent in the seven animals studied ($r = 0.558$). The maximal increase in ventricular fibrillation threshold produced by tocainide was +150 percent; this was achieved at a blood level of 48 μg/ml.

Plotting of the ventricular fibrillation threshold of programmed premature ventricular depolarizations (plotted as percent change from control level) and the simultaneous plasma tocainide concentration revealed a significant increase in the ventricular fibrillation threshold in four of the five animals studied ($r = 0.726$) (Fig. 2). Comparison of these data with the data in Figure 1 shows that, at any given plasma concentration of tocainide, there was a much greater increase in ventricular fibrillation threshold after a premature complex than during sinus rhythm. The maximal increase in ventricular fibrillation threshold produced by tocainide in this series of experiments was +290 percent and was achieved at a plasma concentration of 33 μg/ml.

Effect of tocainide on A-V conduction in the intact heart: The influence of tocainide on cardiac conduction times was investigated. The time intervals between the atrial septal electrogram and His bundle depolarization recorded in the His bundle electrogram was used as an index of conduction time through the atrioventricular (A-V) node. His-Purkinje conduction time was derived from the time interval between the His electrogram and either Q wave in the lead II electrocardiogram or ventricular electrogram (V) recorded in the His bundle electrogram. The interval from the Q wave to the ventricular septal component of the His bundle electrogram ($Q\text{-}V_S$) was used as an index of total ventricular depolarization time. Figure 3 summarizes the effects of tocainide on A-V conduction in five animals. No significant difference was noted between animals anesthetized with pentobarbital or chloralose. The sinus rate remained unchanged during progressive increases in tocainide concentration. A linear depression of A-V nodal conduction was noted during the tocainide infusion. Maximal increases in the A-H interval of 100 to 140 percent over control level were noted at plasma levels of 50 μg/ml. In contrast, conduction in the His-Purkinje system and ventricular muscle was not significantly affected until plasma tocainide concentrations exceeded 40 μg/ml. Both H-V and $Q\text{-}V_S$ intervals remained within 20 percent of control level

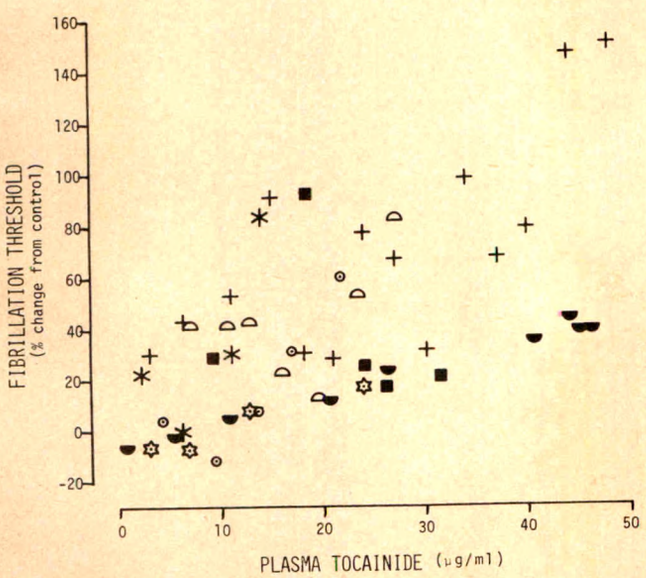


FIGURE 1. Ventricular fibrillation threshold measured in seven dogs during supraventricular rhythm and expressed as a percent of control value (**ordinate**). Plasma tocainide concentration (μg/ml) is on the **abscissa.** Each symbol represents an individual animal. Note the dose-dependent increase in ventricular fibrillation threshold.

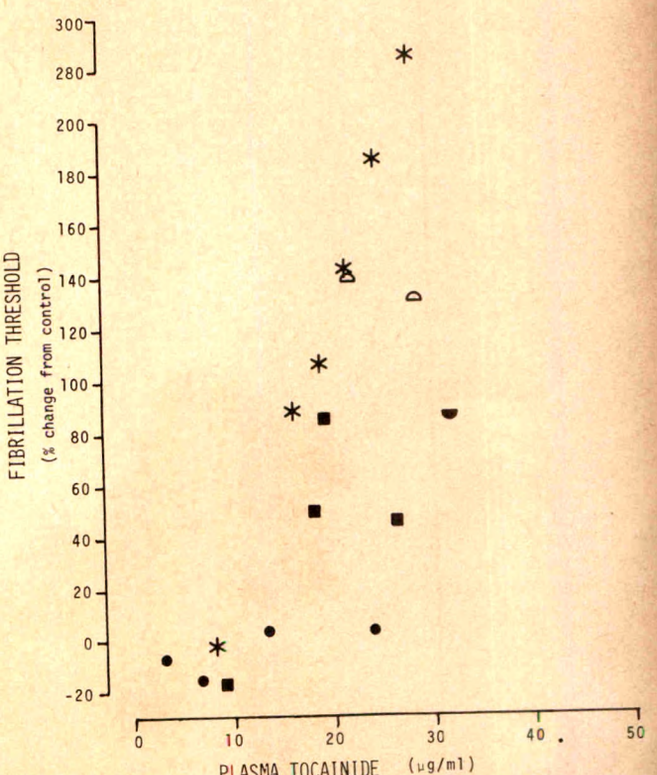


FIGURE 2. Ventricular fibrillation threshold measured in four dogs after premature ventricular depolarizations and expressed as percent of control value **(ordinate).** Plasma tocainide concentration (μg/ml) is on the **abscissa.** Each symbol represents an individual animal. Note that tocainide caused a more pronounced elevation of ventricular fibrillation threshold for premature ventricular complexes than for supraventricular complexes (compare with Fig. 1).

until plasma tocainide concentrations exceeded 40 μg/ml, and then increases of 50 to 100 percent of control were noted in both intervals between 40 and 50 μg/ml.

In Vitro Studies

Effects of tocainide on the electrophysiologic properties of single Purkinje fibers: The typical effects of to-

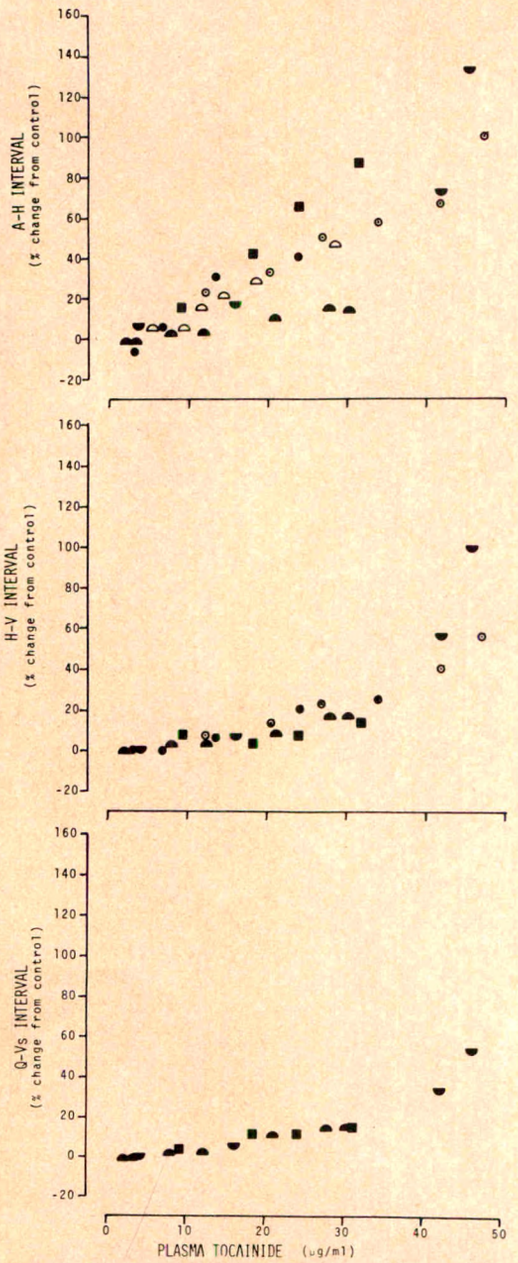


FIGURE 3. Effect of plasma tocainide concentration on intracardiac conduction in five dogs. On the **abscissa,** tocainide concentration is expressed in μg/ml. The A-H interval (indicating atroventricular [A-V] nodal conduction time) is plotted in the **top panel,** the H-V interval (indicating His bundle and bundle branch conduction time) is plotted in the **middle panel** and the Q-V_S interval (indicating total ventricular activation time) is plotted in the **lower panel.** Each symbol indicates an individual animal. Note that there is a dose-dependent linear prolongation of A-V nodal conduction time as plasma tocainide concentration increases. The H-V and Q-V_S intervals remain unchanged until plasma tocainide level increases above 40 μg/ml.

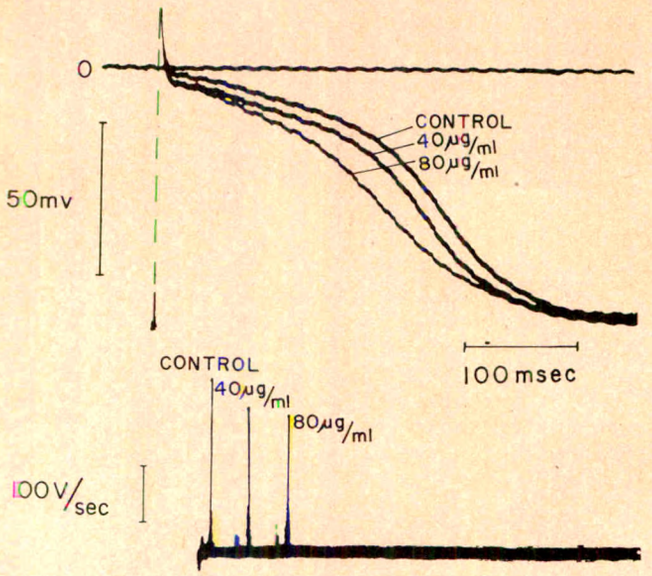


FIGURE 4. Effect of tocainide on Purkinje transmembrane potential from a single Purkinje cell during superfusion with normal Tyróde solution (control) and tocainide (40 and 80 μg/ml). Zero potential line is indicated by 0. The maximal rates of depolarization (v/sec) are shown below the transmembrane potential for the control period (310 v/sec), 40 μg/ml (255 v/sec) and 80 μg/ml (241 v/sec) of tocainide. Note the progressive shortening of action potential duration at 50 percent repolarization and the decrease in rate of depolarization.

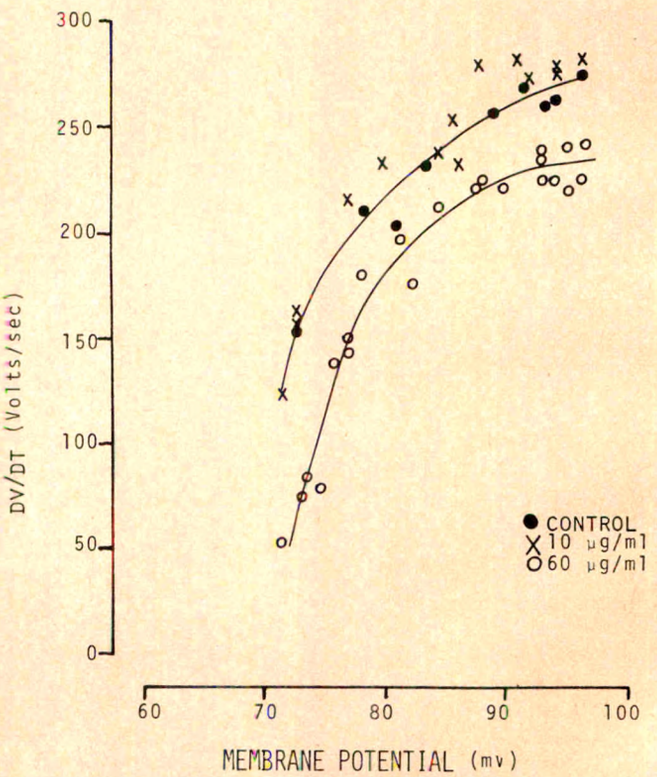


FIGURE 5. Effect of tocainide on membrane responsiveness curve of a single Purkinje fiber. The relation between membrane potential (**abscissa**) and maximal rate of rise of phase O (DV/DT) is plotted for the control period (**closed circles**), and superfusion with tocainide (10 μg/ml, **crosses**) and 60 μg/ml, (**open circles**). Note that tocainide (60 μg/ml) shifted the membrane responsiveness curve downward and to the right.

TABLE III

Effects of Tocainide on Transmembrane Potential Characteristics in 11 Dogs

	Control Period	Tocainide Concentration (μg/ml)				
		1–10	11–20	21–30	31–40	41–50
Dogs (no.)	11	7	11	9	6	4
Resting potential (mv)	83.6 ± 4.8	81.3 ± 6.4	81.1 ± 5.2	80.7 ± 5.3	80.0 ± 3.6	81.2 ± 5.4
Maximal rate of depolarization (v/sec)	329.4 ± 71.5	406.6 ± 156.9	376.6 ± 126.8	296.1 ± 117.3	332.7 ± 59.1	248.7 ± 94.6
Action potential duration at 90% repolarization (msec)	344.8 ± 26.2	304.3 ± 19.3	299.0 ± 47.9	292.0 ± 31.9	327.8 ± 76.5	280.0 ± 35.6
Action potential duration at 50% repolarization (msec)	232.2 ± 22.3	199.7 ± 22.8*	181.3 ± 16.4*	173.0 ± 30.8*	181.0 ± 35.0*	166.0 ± 11.4*
Effective refractory period (msec)	241.2 ± 36.4	215.7 ± 27.9	212.3 ± 16.7*	206.6 ± 42.4	231.8 ± 47.6	204.5 ± 1.7
ERP/APD_{50}	1.05 ± 0.09	1.08 ± 0.09	1.17 ± 0.09*	1.20 ± 0.14*	1.36 ± 0.17*	1.23 ± 0.08*

* Significantly different from control value ($P \leq 0.01$).
ERP/APD_{50} = ratio between effective refractory period and action potential at 50% repolarization.

cainide (40 and 80 μg/ml) on Purkinje action potentials are shown in Figure 4. The amplitude and duration of the plateau phase of the action potential was progressively decreased by increasing tocainide concentration, thereby decreasing the action potential duration measured at 50 percent of full repolarization. This decrease averaged 22, 25 and 29 percent at tocainide concentrations of 20, 30 and 50 μg/ml, respectively. The resting membrane potential, maximal action potential amplitude and total duration for complete repolarization were not significantly changed by tocainide, which also did not significantly decrease the rate of depolarization (dv/dt) of Purkinje fiber action potentials at any concentration. The data for all 11 preparations studied are summarized in Table III. In 10 preparations at tocainide levels greater than 30 μg/ml, the resting membrane potential and maximal action potential amplitude were decreased slightly (less than 10 mv).

The interrelation between the membrane potential at which an action potential is evoked and the rate of depolarization (dv/dt) is often referred to as a membrane responsiveness curve.[9] Figure 5 shows the typical effects of tocainide infusion on this curve in a Purkinje fiber. Membrane responsiveness curves were plotted during the control period and after superfusion with 10 and 60 μg/ml of tocainide. At a concentration of 10 μg/ml no significant difference from control value was observed. At a concentration of 60 μg/ml there was a downward shift in the responsiveness curve so that at any given membrane potential, the rate of rise of the action potential was decreased from control values. In this example the resting potential (the highest points on each curve) remained over −90 mv, and the effective refractory period (lowest points on each curve) remained approximately −73 mv in the presence of tocainide at a concentration of 60 μg/ml.

The effects of tocainide on the membrane responsiveness curve in nine different Purkinje preparations are summarized in Figure 6, in which the maximal degree of displacement of the membrane responsiveness curve along the membrane potential axis is related to the superfusate tocainide concentration. Positive values indicate a shift in the responsiveness curve downward and to the right of control values, and negative values indicate a shift upward and to the left. Tocainide at concentrations of greater than 15 μg/ml consistently shifted the membrane responsiveness curve downward and to the right, as indicated by positive shifts in the responsiveness curve of 5 to 20 mv. At concentrations of less than 15 μg/ml tocainide had inconsistent effects on membrane responsiveness.

The effective refractory period is the earliest interval after a conducted complex in which a second propagated response can be evoked using direct electrical stimulation of three times threshold intensity. Tocainide had no consistent dose-related effect on the effective refractory period of Purkinje fibers (Table III). An increase in the ratio between the effective refractory period and the action potential duration has been

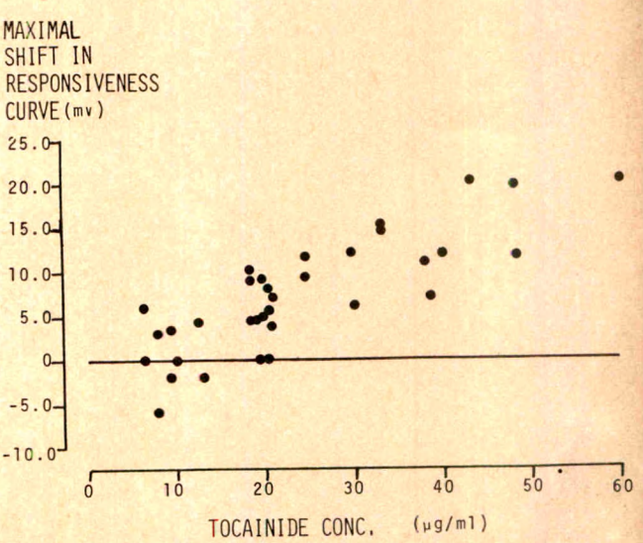


FIGURE 6. Relation between tocainide concentration and shift in membrane responsiveness curve in nine Purkinje preparations. Superfusate tocainide concentration (CONC.) is plotted on the **abscissa** and the maximal shift of the curve on the **ordinate.** A positive shift indicates rightward displacement. Note the dose-related rightward shift of membrane responsiveness.

reported to be associated with cardiac antiarrhythmic activity.[9] In Table III these ratios are shown for the 11 Purkinje fiber preparations studied at increasing tocainide concentrations. There is a consistent dose-related increase in this ratio between tocainide concentrations of 10 to 50 μg/ml.

Effects of tocainide on excitability in single Purkinje fibers: In three preparations, tocainide consistently increased the excitability threshold so that greater current was required to elicit action potentials during repolarization and diastole (Fig. 7). During the control studies, a cathodal transmembrane current of 0.6×10^{-6} amperes was required to excite the single impaled Purkinje fiber during diastole (between 400 and 500 msec on the X axis). When a Purkinje fiber was superfused with tocainide (40 μg/ml), excitation required 1.1×10^{-6} amperes. Increasing the tocainide concentration to 60 μg/ml further increased the current required to evoke an all-or-none action potential during diastole. An increase in current required to excite isolated Purkinje fibers was consistently measured at tocainide concentrations greater than 20 μg/ml. An increased current was also required to excite Purkinje fibers during the repolarization phase (phase 3). During repolarization, a supernormal period of excitability occurs routinely in canine Purkinje fibers perfused in 2.7 mM potassium Tyrode's solution.[10] In the supernormal period, less current is required to evoke an all-or-none response than during diastole. It can be noted in Figure 7 that the supernormal period was shortened but still present when the tocainide concentration was 40 μg/ml. When the concentration was increased to 60 μg/ml, interestingly, the supernormal period of excitability was eliminated. Similar findings were noted in all preparations studied.

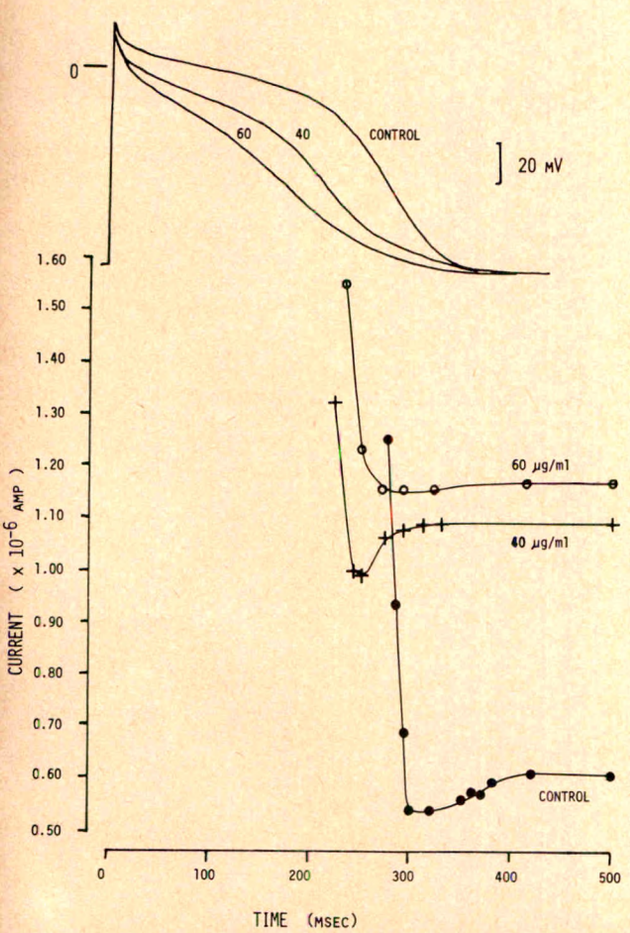


FIGURE 7. Effect of tocainide on Purkinje fiber excitability. The action potentials were recorded during the control period and superfusion with tocainide (40 and 60 μg/ml). The graph below indicates the intracell threshold current required to elicit an all or none action potential of a single fiber during diastole (500 msec) and the relative refractory period (beginning at 400 msec). In the control threshold curve (**closed circles**) there is a supernormal period of excitability. The effects of tocainide on the strength-interval curve is shown for 40 μg/ml (**crosses**) and 60 μg/ml (**open circles**). Note that diastolic threshold is increased in the presence of tocainide, and the supernormal period is eliminated.

Discussion

The need for an orally active antiarrhythmic agent of long duration with minimal side effects that is effective against ventricular arrhythmias is well known. Tocainide (Astra W36095) is a new agent which is both orally active and has a relatively long duration of action. The present investigation performed using both in vivo and in vitro animal models demonstrated that tocainide exhibits significant antiarrhythmic properties. At present, there is no single animal antiarrhythmic model that accurately predicts the efficacy of a compound to suppress ventricular arrhythmias in man. Therefore, we have completed an "electrophysiologic profile" of tocainide using a variety of models. The similarity between the electrophysiologic effects of tocainide and the electrophysiologic effects reported for currently used cardiac antiarrhythmic agents were analyzed for both mechanism of action and relative efficacy.

Tocainide decreases or abolishes arrhythmias due to automaticity enhanced by digitalis cardiotoxicity and myocardial ischemia in the canine model. Currently used antiarrhythmic agents have also been demonstrated to be efficacious in these models.[8,11] The suppression of these arrhythmias was achieved at plasma tocainide concentrations that are therapeutic and nontoxic in the dog. Comparable levels are achievable and acceptable in man.[2]

Effect of tocainide on reentrant arrhythmias: Because there is no well established animal model of a sustained reentrant arrhythmia, our animal studies will not permit a definitive answer to the precise effectiveness of tocainide against reentrant arrhythmias. However, there is a delicate interrelation between conduction time, refractoriness and excitability that determines whether a ventricular arrhythmia due to reentry will persist or terminate. Our studies suggest that tocainide slows conduction of premature beats by its effect on the membrane responsiveness curve. This depression of conduction may be able to convert areas of unidirectional block to bidirectional block, thus making reentry impossible.

Hoffman and Bigger[9] suggested that the increase in the ratio between the effective refractory period and action potential duration found in most antiarrhythmic compounds currently used in man is an important effect. Tocainide consistently increased this ratio as tocainide blood levels increased. As emphasized recently by Rosen et al.,[12] it is plausible to expect that antiarrhythmic agents might exert suppressant action on reentrant arrhythmias if they alter the conduction of

premature responses that might potentially initiate these arrhythmias. The alteration of the ratio between the effective refractory period and action potential duration disrupts the critical relation between conduction and refractoriness that allows the initiation and perpetuation of reentry.

Comparison of tocainide and lidocaine: Tocainide and lidocaine have qualitative similar effects on cell electrophysiology of normal Purkinje fibers. Tocainide, like lidocaine, depresses membrane responsiveness.[12–14] It also shortens the refractory period[14–16] and action potential duration[17–19] and increases the ratio between them.[12] Also, like lidocaine, tocainide affects these changes at clinically achievable and tolerated blood levels.

Effect on A-V conduction: Tocainide has only minimal depressing effects on A-V conduction. Although the effective refractory period of the A-V node is slightly prolonged, at no blood level did tocainide produce A-V block. At tocainide plasma levels at which A-V nodal conduction was slow, there was no detectable depression of conduction within the His-Purkinje system or within the ventricular muscle.

Ventricular fibrillation threshold: The ventricular fibrillation threshold, which measures ventricular electrical stability, was elevated by tocainide. The elevation of threshold measured during normal sinus rhythm was not as great as that observed after the administration of lidocaine.[6] However, tocainide was equally effective as lidocaine in enhancing electrical stability after ventricular premature beats.

Toxicity: The tocainide concentrations employed in both the in vitro and in vivo studies were those found effective in the suppression of arrhythmias caused by digitalis toxicity and myocardial infarction. The toxic effects of up to twice these therapeutic concentrations were also assessed and found to be minimal.

Acknowledgment

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"Ventricular Function Curve" From a Single Diagnostic Left Ventriculogram: Technique, Results and Value

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A programmable atrial pacemaker was used to vary sequential left ventricular end-diastolic volumes. Left ventricular stroke volume and end-diastolic volume were used to construct a left ventricular "function curve." Four successive beats from one diagnostic left ventricular angiogram were analyzed—a beat during atrial pacing at 5 to 10 beats faster than sinus rate, an atrial extrastimulus beat in the sinus nodal reset zone, a post-extrastimulus beat and a sinus beat.

Excluding measurements in postextrastimulus beats, left ventricular stroke volume decreased from 124 to 59 cc ($P < 0.001$) and ejection fraction from 0.67 to 0.52 ($P < 0.001$) as end-diastolic volume decreased from 188 to 123 cc ($P < 0.001$). Mean rate of circumferential fiber shortening was independent of end-diastolic volume but was greater for postextrastimulus beats (1.54 circumferences/sec) than for sinus beats (1.28 circumferences/sec) ($P < 0.001$). Among six patients with increased left ventricular end-diastolic volume (greater than 110 cc/m^2), ejection fraction was abnormal (less than 0.54) in only one patient at increased end-diastolic volume but in three patients at reduced end-diastolic volume, despite a reduced afterload. However, in seven patients with a normal mean rate of circumferential fiber shortening, ejection fraction was normal at both increased and reduced end-diastolic volumes.

This technique is safe and easy to use in man. This study demonstrates that ejection fraction is dependent on end-diastolic volume with rapid changes of R-R interval. Therefore, both ejection fraction and end-diastolic volume should be measured when ejection fraction is used as an index of left ventricular performance, particularly if ejection fractions obtained from different angiograms are being compared.

In 1895, Otto Frank[1] showed that the energy set free in the excited condition (as measured by the tension set up) was proportional to the initial (that is, diastolic) tension on the muscle. In Frank's studies on the frog heart the initial length was proportional to the initial tension. Patterson, Piper and Starling[2] in 1914 demonstrated that in the dog heart there was ". . . a direct proportion between the diastolic volume of the heart . . ." (that is, the length of its muscle fibers) ". . . and the energy set free in the following systole." These classic studies form the basis for the concept of the Frank-Starling mechanism. A relation of different stroke volumes to different end-diastolic volumes was established and, thus, a ventricular function curve was created.

In 1954, Sarnoff and Berglund[3] in their classic studies added another dimension to this concept, demonstrating the presence in an individual ventricle of ". . . a family of Starling or ventricular function curves. . . ." They showed that inotropic agents shifted ventricular function to another curve upward and to the left, whereas ischemia and increased afterload shifted ventricular function to a new curve that was downward and to the right of the control curve. Starling curves are simple in concept

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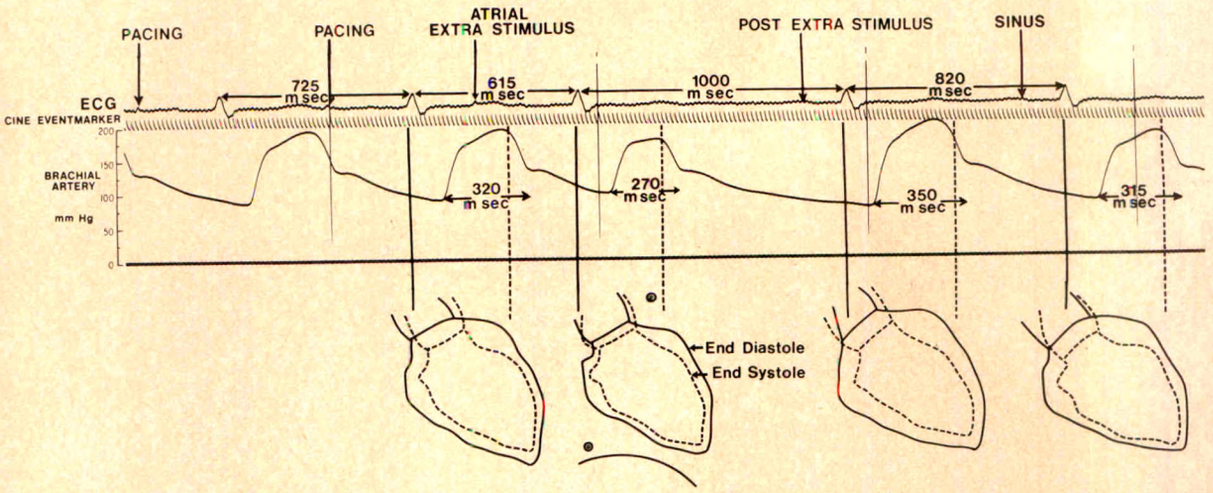


FIGURE 1. Patient 14. Photograph of strip chart record during ventriculography with a programmable atrial pacemaker. The atrial pacemaker controls the R-R interval, and thus influences end-diastolic volume. Peak systolic pressure is lowest for the atrial extrastimulus beat, which also has the smallest volume. ECG = electrocardiogram.

and are probably one of the best means of assessing overall systolic ventricular performance, but they have not found great clinical use as a measure of ventricular performance in man because of difficulties in obtaining different volume measurements and in controlling all hemodynamic functions.

In this paper we describe a method that allows one to obtain several different end-diastolic volumes and stroke volumes from a single diagnostic ventriculogram using a programmable atrial pacemaker. The "ventricular function curve" so obtained may be a modified curve, but it allows assessment of the effects of preload on other indexes of ventricular performance.

Technique

During cardiac catheterization, at the end of the diagnostic hemodynamic study, the right heart catheter was exchanged for a quadripolar pacing catheter that was positioned in the right atrium with a loop that fit snugly against the lateral atrial wall. A programmable atrial pacemaker (manufactured by M. Bloom, Philadelphia, Pennsylvania) was then used to control the R-R interval during left ventriculography, thus effecting changes in ventricular end-diastolic volume. The pacemaker was set (1) to capture the atrium at 5 to 10 beats/min faster than sinus rate for 6 beats, (2) to deliver an atrial extrastimulus (usually 400 msec after the sixth pacing impulse), and then (3) to shut off. The atrial extrastimulus, which was delivered in the sinus nodal reset zone,[4] was followed by the postextrastimulus beat and then a sinus beat. The injection of contrast medium was begun on the third paced beat. Thus, four successive beats (paced, extrastimulus, postextrastimulus and sinus) had different end-diastolic volumes determined in part by diastolic filling time (Fig. 1).

Initial difficulties with this technique included incomplete atrial capture, inappropriate atrial extrastimulus interval and ventricular premature contractions during ventriculography. Continuous atrial capture was assured by meticulous placement of the catheter in the right atrium and a test of atrial pacing in the right anterooblique projection at the end of maximal inspiration. The atrial extrastimulus interval was adjusted before angiography to produce a significant reduction in brachial arterial pressure, which was subsequently noted to correlate well with a significant reduction in end-diastolic volume. Premature ventricular contractions were avoided by careful positioning of the left ventricular catheter and by a long slow injection of contrast material. Success with this technique has continually increased and we now obtain satisfactory data in more than two thirds of patients so studied. Supraventricular tachyarrhythmias have occurred in three patients during this procedure; they were related either to manipulation of the pacing wire or to the atrial extrastimulus beat that occurred by chance in the atrial or sinus nodal echo zones and thus produced a reentrant rhythm.[5,6] These arrhythmias usually terminated spontaneously or with use of an appropriately timed extrastimulus. Although we have not observed it, it is conceivable that the catheter could accidentally slip into the right ventricle and cause a ventricular tachyarrhythmia.

Material and Methods

Data from all 17 patients in whom this technique was successful are presented. They were undergoing diagnostic hemodynamic evaluation in our cardiac catheterization laboratory. Right and left heart catheterization was performed in all patients (Table I). Ventricular volumes were determined during the sequence described from ventriculograms in the right anterior oblique projection obtained at the end of maximal inspiration. Forty-eight to 60 cc of Renografin 76® was injected over 4 seconds starting with the third paced beat. The area-length method of Dodge et al.[7,8] was used for volume calculation in conjunction with an X-Y digitizer. Although biplane techniques are "better," particularly in patients with coronary artery disease, single plane methods are widely used and their limitations understood.[9–12] Brachial arterial pressure, an electrocardiogram and cine event marker were recorded at 200 mm/sec during ventriculography using an Electronics for Medicine recorder (model DR 16) (Fig. 1).

Ejection fraction was determined by dividing the angiographically determined stroke volume by end-diastolic volume. Mean velocity of circumferential fiber shortening was determined by dividing the change in endocardial equatorial

circumference from end-diastole to end-systole, normalized for end-diastolic circumference, by the ejection time. Equatorial circumference was calculated from the minor axis obtained from the formula $M = 4A/\pi L$, where M is the minor axis of the ellipse with area A and long axis L.[7] Ejection time was determined from the simultaneously recorded brachial arterial pressure. The normal value for mean velocity of circumferential fiber shortening is 1.25 circumferences/sec or more and for ejection fraction is 0.54 or more.[13]

Results

The relation of stroke volume to end-diastolic volume in Patient 14 as derived from the data in Figure 1 is shown in Figure 2. Stroke volume and ejection fraction decreased as

TABLE I

Summary of Hemodynamic Data in 17 Patients

Case no.	Age (yr) & Sex	Diagnosis	CI	Pressures $\overline{RA}$	Pressures $\overline{PAW}$	Pressures LV	Pressures BA	EDVI*	EF*	Mean Vcf*
1	42 M	S/P AVR, MR	3.3	3	9	130/10	105/56	150	0.67	1.2
2	56 F	S/P AVR	3.8	3	9	192/9	168/70	85	0.83	1.8
3	60 F	MR	2.4	2	6	205/5	194/82	97	0.58	0.89
4	34 M	S/P resection: Infund. PS	1.9	2	. . .	124/8	130/74	112	0.60	1.2
5	67 M	CAD	2.6	1	7	128/10	130/50	106	0.32	0.46
6	45 M	Small VSD	4.3	0	4	113/9	115/67	130	0.79	1.8
7	61 F	AS	3.5	2	13	190/20	124/64	69	0.88	1.7
8	50 F	CAD	3.3	3	11	180/20	174/74	88	0.82	1.8
9	61 M	AR, CAD	2.8	2	25	198/32	198/70	230	0.46	0.78
10	57 M	Mild AS	2.9	0	4	140/9	130/54	59	0.67	1.2
11	41 F	MS	2.5	2	20	146/4	146/62	92	0.69	1.0
12	65 M	AS	2.2	3	7	216/16	148/66	71	0.71	1.2
13	69 F	HCVD	2.9	1	6	226/10	220/92	98	0.79	2.0
14	57 F	S/P ASD closure	2.8	2	10	204/17	204/82	91	0.52	0.76
15	51M	AR	3.5	1	9	130/10	134/40	150	0.78	1.6
16	62M	CAD	2.9	4	6	196/12	202/105	54	0.66	1.4
17	1F	S/P MVR, AR	2.3	3	11	120/11	120/50	124	0.64	1.0

* Values obtained from sinus beats except in Patient 10, for whom the paced beat values are given because of poor opacification of the sinus beat.

AR = aortic regurgitation; AS = aortic stenosis; ASD = atrial septal defect; AVR = aortic valve replacement; BA = brachial arterial pressure (mm Hg); CAD = coronary artery disease; CI = cardiac index (liters/min per m^2); EDVI = end-diastolic volume index (cc/m^2); EF = ejection fraction; HCVD = hypertensive cardiovascular disease; Infund. = infundibular; LV = left ventricular pressure (mm Hg); MR = mitral regurgitation; MS = mitral stenosis; MVR = mitral valve replacement; PAW = pulmonary arterial wedge pressure (mm Hg); PS = pulmonary stenosis; $\overline{RA}$ = mean right atrial pressure (mm Hg); S/P = status post; Vcf = mean velocity of circumferential fiber shortening (circumferences/sec); VSD = ventricular septal defect.

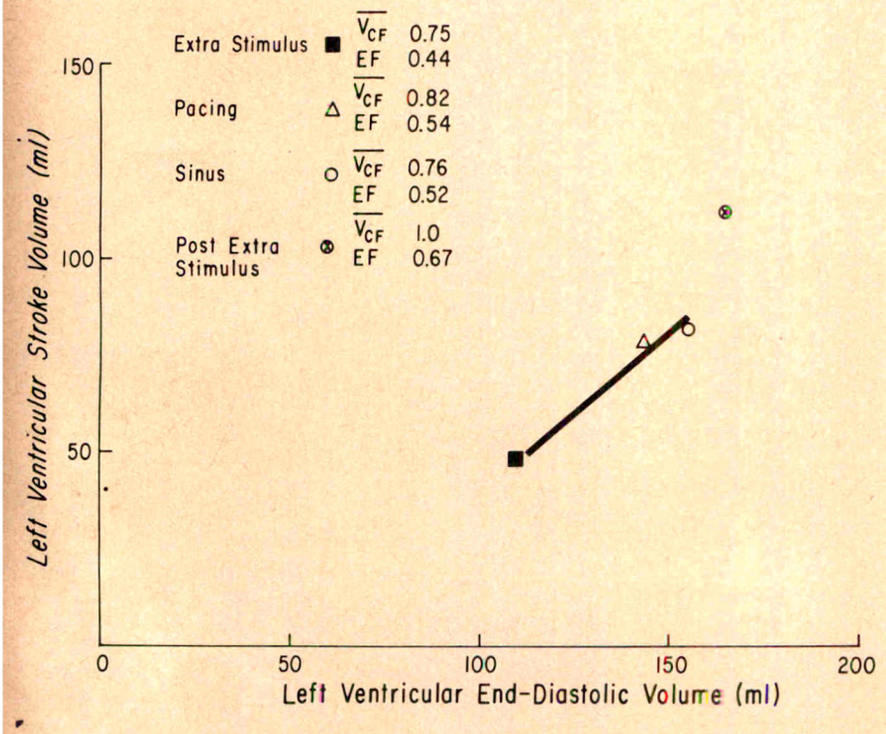


FIGURE 2. Patient 14. Left ventricular function curve. Stroke volume decreases as end-diastolic volume decreases. Ejection fraction (EF) decreases with end-diastolic volume, while mean velocity of circumferential fiber shortening (Vcf) in circumferences/sec remains relatively constant. Both ejection fraction and mean Vcf increase with the postextrastimulus beat.

end-diastolic volume decreased. Mean velocity of circumferential fiber shortening was independent of end-diastolic volume. However, both mean velocity of circumferential fiber shortening and ejection fraction increased with a postextrastimulus beat. Postextrastyolic potentiation has been well demonstrated in both laboratory animals[14,15] and man.[16,17] In all patients the postextrastimulus beat was excluded from construction of the "function curves" (Fig. 3). The slopes of the curves relating stroke volume and end-diastolic volume were similar in most subjects, irrespective of end-diastolic volume. The relation of ventricular stroke work to end-diastolic volume in patients without a left ventricular outflow gradient is shown in Figure 4. The curves are similar to those relating stroke volume to end-diastolic volume.

The effect of end-diastolic volume on ejection fraction for all 17 patients is shown in Figure 5. Ejection fraction from beats recorded at the largest volume in each patient (postextrastimulus beat excluded) was significantly (P <0.001) greater than that for beats recorded at small volumes. However, mean velocity of circumferential fiber shortening was

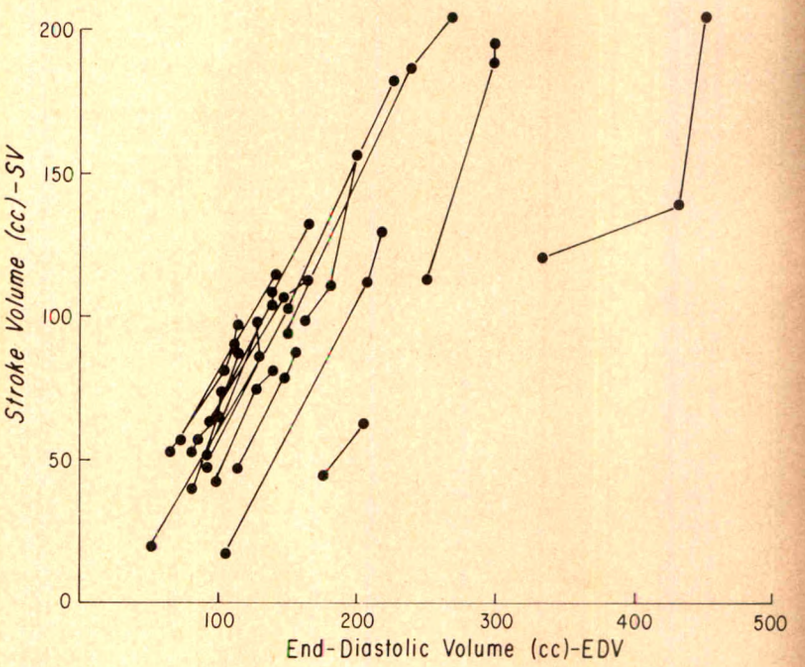


FIGURE 3. Left ventricular function curves for all 17 patients (postextrastimulus beat excluded in all patients). The decrease in stroke volume (SV) with a decrease in end-diastolic volume (EDV) is almost linear. The angular shape of the function curve of the largest ventricle may represent reduced afterload or geometric alteration resulting in improved performance at a smaller end-diastolic volume.

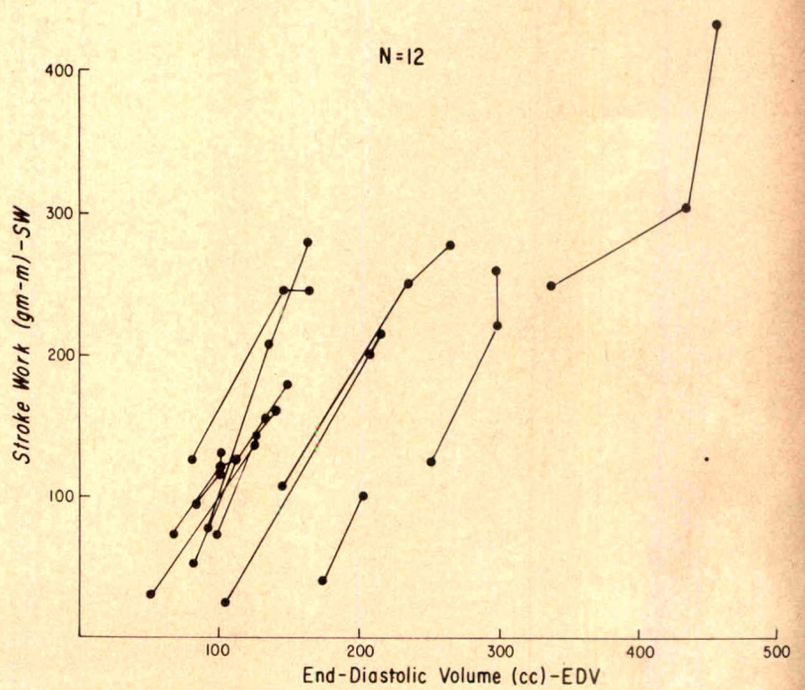


FIGURE 4. Relation of left ventricular stroke work (SW) to end-diastolic volume (EDV) (post-extrastimulus beat excluded) in 12 patients. Patients with a left ventricular outflow gradient were excluded because brachial arterial pressure and left ventricular pressure are not identical in such patients, and the latter was not measured during angiography. The curves are similar to those depicted in Figure 3. N = number of patients.

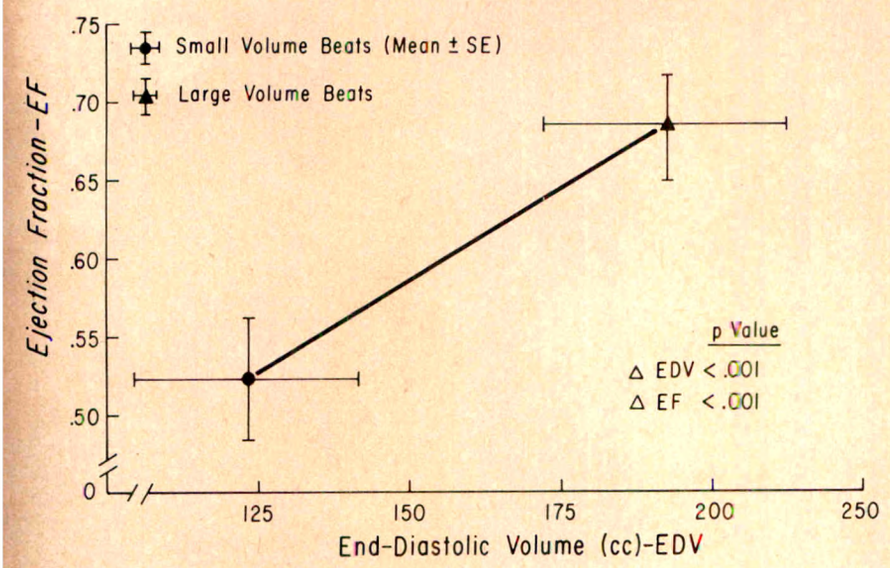


FIGURE 5. Effect of end-diastolic volume (EDV) on ejection fraction (EF). The ejection fractions of the beats with the largest and smallest volumes (postextrasystolic beats excluded) are compared for each patient. Ejection fraction decreased significantly with smaller end-diastolic volumes. SE = standard error; p = probability.

not significantly affected by end-diastolic volume (Fig. 6). These findings suggest that changes in contractility were not the basis for the observed volume-related changes in ejection fraction.

Because ejection fraction is dependent on end-diastolic volume, it might vary importantly in ventricles that vary considerably in size. To test the latter hypothesis, the relation of ejection fraction and end-diastolic volume in large and small volume beats under conditions of pacing-induced changes in end-diastolic volume was examined in patients with normal and increased volume (more than 110 cc/m^2 in the sinus beats)[13] and with abnormal and normal mean velocity of circumferential fiber shortening (1.25 circumferences/sec or more in the sinus beats). In all four subgroups ejection fraction decreased significantly with end-diastolic volume (Fig. 7). However, in all patients with normal mean velocity of circumferential fiber shortening, ejection fraction remained normal at both high and low volumes. In contrast, ejection fraction was normal in five of six ventricles with an increased end-diastolic volume index (cc/m^2) at large volumes but in only three of six ventricles at smaller volumes. Thus, two patients who had a normal ejection fraction at a large end-diastolic volume had an abnormally low ejection fraction at reduced end-diastolic volume. End-systolic volumes varied from beat to beat in all patients.

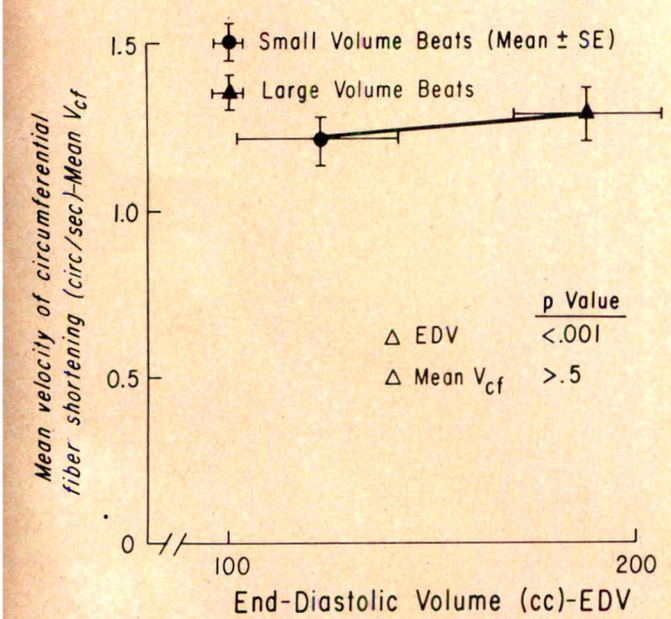


FIGURE 6. Effect of end-diastolic volume (EDV) on mean rate of circumferential fiber shortening (Vcf). The beats with the largest and smallest volumes (postextrasystolic beats excluded) are compared for each patient. Mean Vcf did not vary significantly with end-diastolic volume. circ = circumferences; p = probability.

Discussion

End-diastolic volume is a complex function of diastolic filling time, previous end-systolic volume and left atrial transport function in combination with left ventricular diastolic pressure-volume relations. We were able to regulate end-diastolic volume by changing R-R intervals with a programmable atrial pacemaker (Fig. 8). Thus, serial end-diastolic volumes were obtained from a single diagnostic ventriculogram from which the relation of stroke volume to end-diastolic volume was derived. As noted by Sarnoff and Berglund,[3] there is a family of function curves that depend on contractility and afterload. In this study, *contractility* and *afterload* were not controlled, and thus the *"function curve" obtained may actually be a composite of several different function curves that were closely related to each other;* in other words, it may be a "modified" function curve.

Ventricular performance during paced, sinus and extrastimulus beats: Factors that might have affected *contractility* in our study include the strength-interval relation and the effect of the injected contrast medium. Karliner et al.[18] evaluated ventricular performance in atrial fibrillation where changes in R-R interval are continually present and found little effect of the strength-interval relation on ventricular performance. Their hypothesis is supported by our finding that mean velocity of circumferential fiber shortening

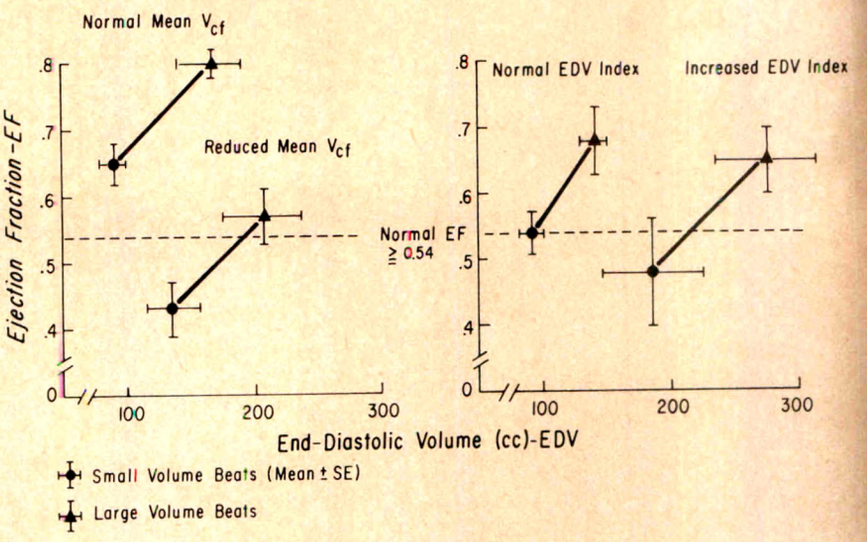


FIGURE 7. Effect of end-diastolic volume on ejection fraction (EF). The patients were separated into four subgroups according to mean rate of circumferential fiber shortening (V_{cf}) in circumferences/sec and end-diastolic volume (EDV) index of the sinus beat: normal and reduced mean Vcf and normal and increased (110 cc/m^2 or more) EDV index. Ejection fraction increased with end-diastolic volume in all groups. In patients with normal mean Vcf, ejection fraction was normal at large and small end-diastolic volumes. In patients with increased EDV index, ejection fraction was normal in five of six patients at large end-diastolic volumes, but only in three of six patients at small end-diastolic volumes. SE = standard error of the mean.

did not change significantly among paced, sinus and extrastimulus beats. However, predictably, when there was a marked decrease in R-R_1/R-R_2 (where R, R_1 and R_2 are three consecutive beats), as with the postextrastimulus beat, there was significant potentiation of mean velocity of circumferential fiber shortening (mean velocity of circumferential fiber shortening averaged 1.54 for postextrastimulus beats and 1.28 for sinus beats; $P < 0.001$).

Neither residual potentiation of the sinus beat nor suppression of the extrastimulus beat as estimated from mean velocity of circumferential fiber shortening was observed. Although we excluded the postextrastimulus beat from construction of the "ventricular function curve," it could be used to uncover reversible wall motion abnormalities[19] and residual ventricular function.[20] In many of the cited studies,[15,16,19,20] postextrasystolic potentiation related to ventricular premature beats. In our study we used atrial extrastimuli and found postextrasystolic potentiation. Postextrasystolic potentiation was demonstrated previously with atrial premature beats.[17]

Postextrasystolic potentiation and its persistence: Experimental data indicate that postextrasystolic potentiation persists for several beats after a premature beat.[14] In our studies, mean velocity of circumferential fiber shortening in the sinus beats was the same as in the paced beats, suggesting that residual potentiation did not persist after the potentiated beat. We also examined this relation in two additional patients by recording left ventricular pressure and its first derivative and calculating maximal velocity of contractile element shortening (Vmax) (values from one patient are shown in Table II). Maximal velocity of contractile element shortening in the paced and sinus beats was the same and the findings reproducible.

The reasons for the difference between our findings and those of experimental studies are not clear. Postextrasystolic potentiation and its persistence is partly a function of how closely the premature beat followed the last regular beat and also of interval from the premature beat to the first subsequent beat.[14] Although postextrasystolic potentiation occurs with premature ventricular[14–16,19,20] and atrial beats,[17] the mode of action is more than a Frank-Starling effect and it may not be physiologically correct to equate the two types of extrasystoles. Our use of atrial extrastimuli

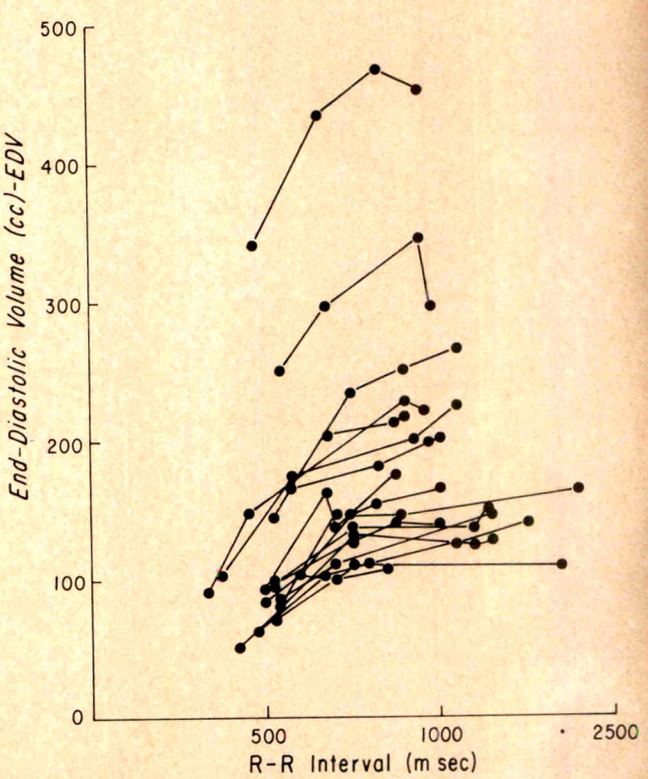


FIGURE 8. Effect of R-R interval on end-diastolic volume (EDV) in 17 patients. The R-R interval was controlled with a programmable atrial pacemaker. Volume decreased with a decrease in R-R interval at an increasing rate. For some beats, end-diastolic volume did not increase with the longer R-R intervals, reflecting the other factors (previous end-systolic volume, atrial transport function, left ventricular diastolic pressure-volume relation) influencing end-diastolic volume.

TABLE II

Maximal Velocity of Contractile Element Shortening (Vmax) in Two Cycles Obtained Within a Few Minutes of Each Other

Beat	First Cycle		Second Cycle	
	R-R Interval (msec)	Vmax (ML/sec)	R-R Interval (msec)	Vmax (ML/sec)
Atrial paced	135	0.75	135	0.67
Atrial paced	135	0.75	135	0.72
Atrial paced	135	0.74	135	0.74
Atrial paced*	135	0.76	135	0.71
Atrial extrastimulus*	90	0.66	94	0.62
Post extrastimulus*	173	0.87	177	0.86
Sinus*	160	0.72	162	0.72
Sinus	155	0.72	162	0.74
Sinus	154	0.74	160	0.76

* These four beats are similar to those obtained during the left ventriculogram.

ML = muscle lengths; Vmax = maximal velocity of contractile element shortening.

rather than the ventricular premature beats used by previous investigators[14] may be another reason why we did not see persistence of postextrasystolic potentiation in the sinus beats. Also, the amount of postextrasystolic potentiation in our patients was quite modest (20 percent) (mean velocity of circumferential fiber shortening in potentiated beats averaged 1.54 and in sinus beats 1.28 circumferences/sec). Mean velocity of circumferential fiber shortening and maximal velocity of contractile element shortening in the paced beats were not higher than in the sinus beats in our study. This may have been an effect of our rate of atrial pacing, which was only 5 to 10 beats faster than sinus rate.

Ventricular performance and contrast medium: In man, depression of left ventricular function with contrast medium cannot be demonstrated "late" (2 or more minutes) after injection of contrast medium into the left ventricle.[21] More relevant to this study are the early effects of contrast medium. In a beat by beat analysis of the effects of contrast medium, Karliner et al.[22] showed no significant change in maximal rate of rise of left ventricular pressure (dP/dt) with abnormal ventricles, but a 15 percent decrease in maximal dP/dt by the eighth beat in normal ventricles. Hammermeister and Warbasse[23] could detect no significant change in ventricular volume and ejection fraction up to five beats after injection of contrast medium into the left ventricle. However, Carleton,[24] using a rapid injection of a large amount of contrast agent (30 cc/sec), noted significant elevation of end-diastolic volume and end-systolic volume after three opacified cycles; interestingly, the ejection fraction did not change during this period. In our study, mean velocity of circumferential fiber shortening did not change from beat to beat except with postextrasystolic potentiation. Also, ejection fraction increased with time (as did volume) rather than decreasing, as would be expected during a depression of left ventricular function induced by contrast medium. For all of these reasons we believe that the observed changes in ejection fraction reflected the respective end-diastolic volume rather than the effect of contrast medium on left ventricular performance.

Ventricular performance and changes in afterload: Afterload is a complex measure that is best approximated in the intact ventricle by instantaneous systolic ventricular wall stress.[25] The factors influencing ventricular wall stress are intracavitary pressure, internal radius and wall thickness.[26] In the dog, with constant end-diastolic volume and wall thickness, Ross et al.[27] showed that aortic pressure was the major determinant of afterload and thus of ventricular performance. In our study, both volume (and thus radius and wall thickness) and pressure changed from beat to beat. Volume and peak systolic pressure were lowest in beats with a short R-R interval. Afterload should have been greatest in beats with a long R-R interval and least in those with a short R-R interval. If afterload were exerting a major influence on the changes in ventricular performance in our study, then the expected result would be an increase in ejection fraction as R-R intervals (and thus volume and pressure) decreased. The opposite result was seen; namely, ejection fraction increased as end-diastolic volume became larger, suggesting that preload was the major determinant of ventricular performance during these hemodynamic manipulations.

Ventricular performance and changes in preload: The dependence of ejection fraction on preload in man has been controversial. Using a tilt table and echocardiographically derived volumes, Rankin et al.[28] found no significant effect of end-diastolic volume on ejection fraction in 10 normal subjects. Quinones et al.[29] found that infusion of dextran increased echocardiographically determined end-diastolic volume and ejection fraction. In both of these studies and in the experimental study of Mahler et al.,[30] mean velocity of circumferential fiber shortening was independent of preload. Karliner et al.[18] showed that in patients with atrial fibrillation, both ejection fraction and mean velocity of circumferential fiber shortening varied with end-diastolic volume. However, in the dog, Mitchell et al.[31] found that ejection fraction clearly was a function of end-diastolic volume. Their study used endocardial beats with biplane cinefluorography to determine ventricular volume while preload was manipulated and heart rate, aortic pressure and inotropic state were held constant.

Ejection fraction and end-diastolic volume: Our study strongly supports the concept that ejection fraction is partly a function of end-diastolic volume. Ejection fraction thus must be considered with respect to the volume at which it is measured. This may apply particularly to patients with regurgitant lesions for whom valve replacement therapy is being considered. In this setting, ejection fraction may decrease precipitously from normal to abnormal as end-diastolic volume is reduced after correction of valve regurgitation, negating any hemodynamic benefit that may be derived from valve replacement. In other words, in some patients,

preoperatively increased ventricular volume may mask reduced ventricular performance assessed only from ejection fraction, as shown by two of our patients. This latent poor ventricular performance in patients with increased end-diastolic volume and normal ejection fraction may be uncovered by a ventricular function curve as shown in our study, or by using mean velocity of circumferential fiber shortening, a measure of ventricular performance that appears to be less dependent upon end-diastolic volume.

Clinical implications: A modified ventricular function curve relating end-diastolic volume and stroke volume can be created in man during a single diagnostic ventriculogram with use of a programmable atrial pacemaker. Analysis of the function curve shows that *ejection fraction is dependent on end-diastolic volume,* particularly in large ventricles. Mean velocity of circumferential fiber shortening did not change significantly with end-diastolic volume. Studies using ejection fraction as an index of ventricular performance must consider the volume at which ejection fraction is measured, particularly with rapid changes of R-R interval and when ejection fractions obtained from different angiograms are being compared.

Potential uses of this technique that need to be evaluated include (1) assay of the effects of pharmacologic or surgical therapy, (2) detection of latent impaired left ventricular function in patients with increased end-diastolic volume and normal ejection fraction, and (3) detection of reversible wall motion abnormalities and residual ventricular function with use of the postextrastimulus beat.

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Quantitative Radionuclide Angiography in the Right Anterior Oblique View: Comparison With Contrast Ventriculography

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Because the right anterior oblique view is widely accepted as the best "single" projection for assessing wall motion, the utility of this view during first pass radionuclide angiography was studied in 44 patients who also underwent contrast ventriculography and coronary arteriography. Of the 44 patients, 8 had a normal heart and 14 had coronary artery disease with normal wall motion on contrast ventriculography. All also had normal contraction on radionuclide angiography. On contrast ventriculography, 22 patients had coronary artery disease and asynergy involving 34 left ventricular segments. Of 17 segments localized to the anterior and apical asynergic areas on contrast ventriculography, 16 were accurately localized with radionuclide angiography. Similarly, of 17 inferior asynergic areas, 13 were also shown to be inferior on radionuclide angiography. In addition, quantitative assessment of the severity of asynergy using the hemiaxis method demonstrated a good correlation between asynergic severity as defined with radionuclide angiography and contrast ventriculography. Of 11 anterior areas, 7 defined as hypokinetic with contrast ventriculography demonstrated chordal shortening of 20.1 ± 5.2 percent (mean ± standard error of the mean) ($P < 0.005$ compared with normal) on radionuclide angiography. Similarly, four akinetic or dyskinetic segments on contrast ventriculography demonstrated a greater reduction (4.0 ± 4.0 percent) in chordal shortening on radionuclide angiography ($P < 0.05$ compared with hypokinetic segments). Akinetic apical and inferior segments as defined with contrast ventriculography also showed a marked reduction in wall motion to 10.4 ± 7.3 percent and 7.5 ± 4.1 percent, respectively.

After appropriate background subtraction, determination of ejection fraction using radionuclide angiography showed a correlation of 0.839 between the left anterior oblique and right anterior oblique projections independent of the sequence of injection. In addition, ejection fraction determined with radionuclide angiography in the left ($r = 0.824$) and right ($r = 0.801$) anterior oblique views correlated well with ejection fraction assessed from contrast ventriculography. Thus, first pass radionuclide angiography performed in the right anterior oblique view is a sensitive noninvasive means of assessing the location and severity of asynergy as well as global left ventricular performance in patients with coronary artery disease.

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Assessment of the pattern of left ventricular contraction is a vital part of the evaluation of patients with coronary artery disease. It has clearly been shown that contraction disorders are important prognostically in patients treated medically[1,2] and are the most important determinants of both the risk and benefit of coronary bypass surgery.[3–5] Although contrast ventriculography has provided the only means of accurately

assessing both regional and global left ventricular function in these patients, increasing attention has focused on a noninvasive means of evaluating left ventricular performance using radioactive tracer techniques. Gated blood pool studies[6–8] have provided useful information on wall motion and global ejection fraction in the left anterior oblique or anteroposterior view. However, because this technique requires accumulation of radioactive counts during the phase of equilibrium when isotope is simultaneously present in both the right and the left ventricle, visualization of the inferior and anterior areas is suboptimal.[9]

In contrast, the first pass technique accumulates radioactive counts on the initial passage of the isotope as it traverses the right heart, lung, left atrium and left ventricle. Early studies have shown that left ventricular ejection fraction can be accurately determined using time-activity curves generated on the basis of passage of isotope through the left ventricle.[10–12] In addition, this technique permits temporal separation of the right and left ventricle.[10–12] The method thus obviates the problem of anatomic overlap of the right and left ventricles in the right anterior, apical and inferior segments along the long axis of the left ventricle.

In this study, first pass radionuclide angiography in the right anterior oblique view was compared with contrast ventriculography in the assessment of both regional wall motion and ejection fraction in patients undergoing evaluation for coronary artery disease.

Methods

Selection of patients: The study group comprised 44 patients admitted for evaluation of heart disease who underwent cardiac catheterization, contrast ventriculography and coronary arteriography and gave informed consent for radionuclide angiographic studies. On the basis of results of cardiac catheterization, coronary arteriography and contrast ventriculography, patients were classified as having (1) a normal heart; (2) coronary artery disease (75 percent or greater obstruction of luminal diameter in one of the three major coronary arteries) with normal left ventricular segmental wall motion; or (3) coronary artery disease with asynergy. Patients with valve, congenital or primary myocardial disease were excluded from the study.

Radionuclide angiograms: Within 24 hours of catheterization, radionuclide angiograms were obtained using a computerized multicrystal scintillation camera (Baird Atomic System Seventy-Seven) and a 1 inch (2.54 cm) thick parallel hole collimator. An 18 gauge percutaneous intravenous catheter was placed in an antecubital vein. After administration of 20 mg of potassium perchlorate, the patient was positioned in either the right or left anterior oblique view, and a 12 to 18 millicurie (mCi) dose of technetium-99m pertechnetate in a volume less than 0.8 cc was rapidly administered and flushed with 10 to 15 cc of 5 percent dextrose in water to obtain a bolus injection. Counts were recorded at a framing interval of 50 msec (20 frames/sec) during the first pass of the isotope. Data were recorded on computer disc for processing and magnetic tape for long-term storage. After 5 to 10 minutes, the patient was positioned in the next view to be obtained (either right or left anterior oblique) and a background frame collected. Within 30 seconds of obtaining the background frame, a second injection of pertechnetate was administered and recorded as for the first injection. Data acquisition required less than 30 seconds for each view and resulted in 50,000 to 750,000 counts whole image during the phase when isotope was present in the left ventricle. The maximal total dose of pertechnetate given to any patient was 35 mCi or less.

Right and left heart catheterization: This procedure was performed using standard techniques.[13,14] After measurement of left ventricular pressure (using Statham P23Db transducers) and cardiac output (dye-dilution method using indocyanine green), contrast left ventriculography was performed in the right anterior oblique projection using 30 to 40 cc of meglumine diatrizoate (Renografin-76®) injected into the left ventricle. Selective coronary cinearteriography was performed in multiple views using the Judkins technique. Cines were taken on a 10 by 6 inch (25.4 × 10.2 cm) dual field image intensifier (Siemens) at 64 frames/sec using 35 mm Kodak Shellburst film. Hemodynamic data (aortic and left ventricular pressures) were monitored and recorded on an Electronics for Medicine oscillographic recorder.

Analysis of angiographic data: All radionuclide angiography data were first corrected for nonuniformity of field by automatically correcting each frame of data for differences between individual crystals using a uniform source obtained each day. This resulted in each crystal demonstrating a uniform response to gamma emissions. In addition, a dead time correction was applied. In the case of the second radionuclide angiogram, the background frame obtained immediately before the second study was automatically utilized by the computer to correct each frame of data for preexisting counts on a crystal for crystal basis. Corrected data were analyzed after redisplaying the data at intervals of 100 msec.

A region of interest was selected comprising the left ventricle using a zone grid representing the individual crystals. A time-activity curve was then generated that displayed counts/100 msec recorded by the "flagged" crystals. This resulted in a series of peaks (diastole) and valleys (systole) that were utilized to derive a computer-generated representative cycle. This cycle could then be played in real time to analyze qualitatively the contraction pattern of the left ventricle. In addition, computer-derived images of end-diastole, end-systole and superimposed perimeters of end-diastole and end-systole were utilized to provide a quantitative index of wall motion using the hemiaxis method (Fig. 1). This procedure was similar to the analysis used for the contrast ventriculo-

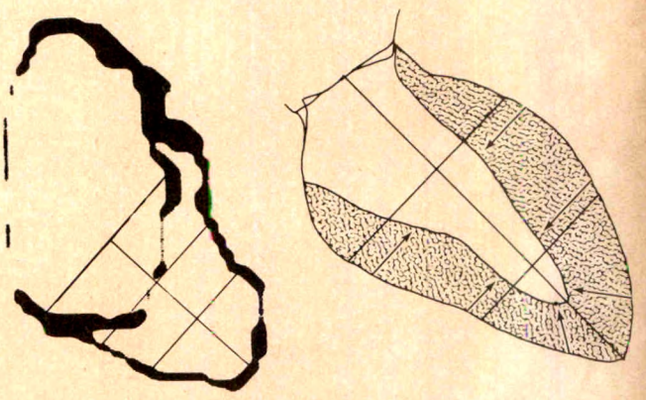


FIGURE 1. Left, superimposed radionuclide angiographically derived end-diastolic and end-systolic perimeters showing normal segmental wall motion. **Right,** superimposed outline of diastolic and systolic phases of left ventricular contraction based on contrast ventriculography in the same patient.

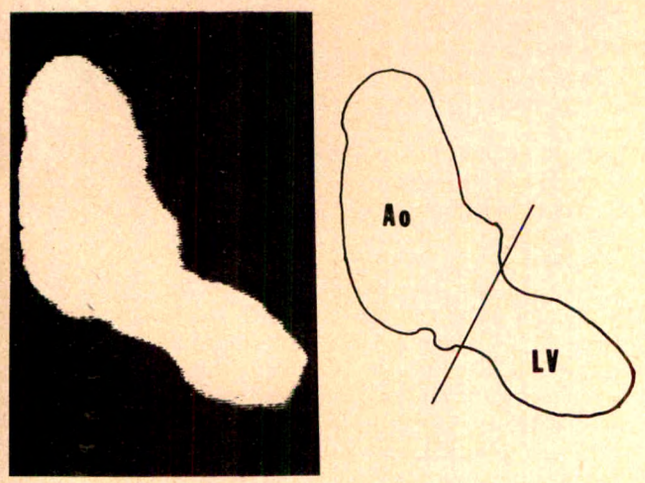


FIGURE 2. Computer-derived radionuclide angiographic end-diastolic frame. Note the well defined aortic valve plane (**diagonal line**) as diagrammed. Ao = aorta; LV = left ventricle.

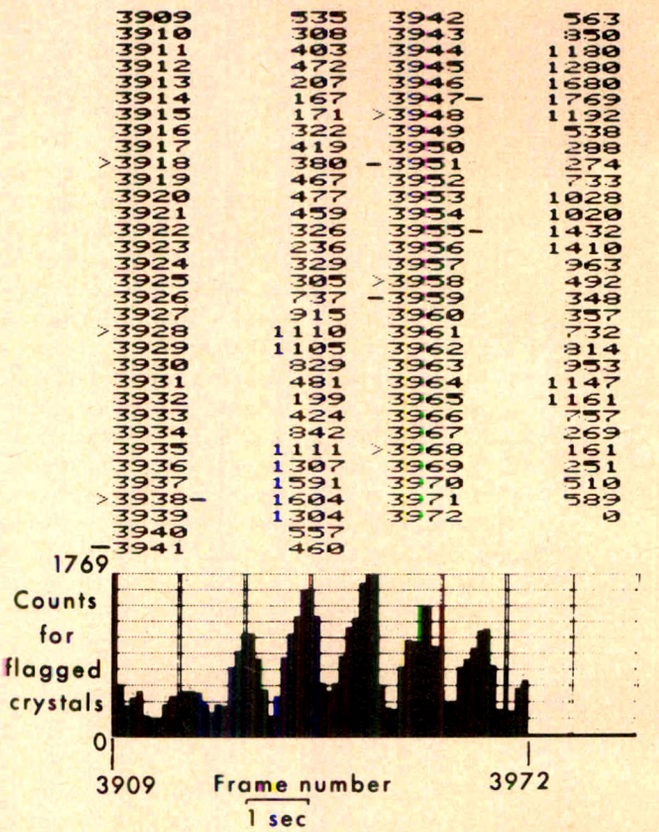


FIGURE 3. Time-activity histogram showing left ventricular phase after 35 percent background subtraction. Ejection fraction computed by three peak method using labeled frames was 0.77 (see text for details).

grams as previously described.[13–15] End-diastolic and end-systolic frames were traced and the aortic valve plane was demarcated. A line connecting the mid point of the aortic plane and the apex was drawn and the end-diastolic and end-systolic frames were superimposed. Hemiaxes were drawn that trisected the long axis at right angles, and each hemiaxis was measured and recorded as a percent change from end-diastole to ascertain the amount of regional contraction.

Asynergy for contrast ventriculography was classified as follows: normal contraction, greater than 25 percent hemiaxis shortening by comparison with data based on a series of normal patients[13,14]; hypokinesia, less than 25 percent hemiaxis shortening; akinesia, 0 to 5 percent hemiaxis shortening; and dyskinesia, paradoxical systolic expansion.[13,14] The location and severity of asynergy were assesed independent of knowledge of the radionuclide angiographic data.

Ejection fraction was obtained from the right anterior oblique view using the area-length formula of Sandler and Dodge[16] and corrected using the regression equation of Kennedy et al.[17]

Significant coronary obstructive disease was considered present if there was 75 percent or more stenosis of the luminal diameter of the left main, left anterior descending, left circumflex or right coronary.[13,14]

Determination of ejection fraction from radionuclide angiograms was based on the change in counts from diastole to systole; that is, $(C_D - C_S)/(C_D - b)$ where C_D = counts in diastole, C_S = counts in systole and b = background. This procedure assumes accurate assessment of background (b) during the left ventricular phase which during the first pass in the left anterior oblique view comprises primarily left atrium and lung as well as scattered radiation.[9] In the left anterior oblique view, no significant overlap of the right and left ventricles occurs. Thus, for this view, a background frame was chosen that represents the distribution of activity just before arrival of isotope into the left ventricle. Preliminary data[18,19] have shown an excellent correlation between radionuclide angiography in the left anterior oblique view and angiographically derived ejection fraction.

For the right anterior oblique view, ejection fraction was derived as follows: Utilizing the computer-generated end-diastolic frame, the region of the left ventricle was "flagged" using a zone grid and the counts displayed as a time-activity curve (counts/100 msec). Accurate depiction of the aortic valve plane in this view was possible, as previously reported,[8,9] thus avoiding counts over the aorta (Fig. 2). Accuracy of flagging was also checked by use of a computer-generated frame that delineates the region surrounding the ventricle. This helped to avoid inadvertent flagging of lung tissue. Background subtraction ranging from 30 to 50 percent in 5 percent increments was applied in all patients. The newly derived time-activity curves obtained after background subtraction were utilized to determine ejection fraction from three peaks (diastole) and three valleys (systole). The maximal peak and the one immediately before and after this peak were utilized (Fig. 3). This provided an ejection fraction based on an average of 6,221 counts (range 3,723 to 10,268) for the three end-diastolic peaks after background subtraction.

Statistical analysis was performed using Student's *t* test for paired and unpaired data and least squares fit for determination of regression equation. All values are given as mean ± standard error of the mean.

Results

Of the 44 patients, 8 had a normal heart, 14 had coronary artery disease (average of 1.9 obstructed vessels) with normal left ventricular contraction and 22 had

TABLE I

Comparison of Localization of Asynergy

Radionuclide Angiography	Contrast Cineventriculography		
	Anterior	Apical	Inferior
Anterior	11	1	0
Apical	0	5	0
Inferior	0	0	13
None	0	0	4

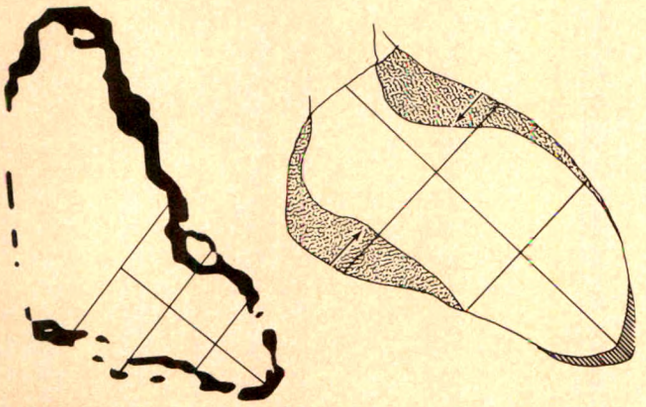


FIGURE 4. Comparison of radionuclide angiographic end-diastolic and end-systolic perimeters in the right anterior oblique view with contrast ventriculographic wall motion analysis. Segmental akinesia of the anterior segment and dyskinesia of the apical segment with preservation of inferior and anterobasal wall motion (**arrows**) is clearly depicted by both techniques.

coronary artery disease (average of 2.5 obstructed vessels) with segmental asynergy.

Segmented wall motion: All eight patients with both angiographically normal coronary arteries and normal left ventricular contraction on contrast ventriculography in the right anterior oblique view also demonstrated normal wall motion on radionuclide angiography (Fig. 1). Similarly, all 14 patients with coronary artery disease and normal contrast ventriculographic segmental motion in the right anterior oblique view also manifested normal contraction in all segments on radionuclide angiography.

Twenty-two patients demonstrated asynergy involving 34 segments (Table I). A close correlation was found between the location of asynergy as depicted by contrast ventriculography and radionuclide angiography. Of 11 anterior and 6 apical segments showing asynergy on contrast ventriculography, 11 and 5, respectively, also manifested asynergy on radionuclide angiography of the corresponding areas (Fig. 4). One area of apical asynergy on contrast ventriculography was considered to show anterior asynergy with radionuclide angiography. Of 17 inferior asynergic areas on contrast ventriculography, 13 manifested asynergy on radionuclide angiography (Fig. 5), whereas 4 appeared normal.

TABLE II

Assessment of Severity of Asynergy With Radionuclide Angiography (mean ± standard error of the mean)

Contrast Angiography	Radionuclide Angiography (% shortening)		
	Anterior	Apical	Inferior
Normal (8 patients) (>25% hemiaxis shortening)	70.1 ±9.6	48.3 ±7.3	62.2 ±6.9
Coronary artery disease			
No asynergy (14 patients)	58.4 ±5.7	41.1 ±4.2	57.9 ±7.5
Asynergy (22 patients)			
Hypokinesia (<25% hemiaxis shortening)	20.1 ±5.2 (7)*	11 (1)	17.2 ±6.5 (5)*
Akinesia/dyskinesia (<5% hemiaxis shortening)	4.0 ±4.0 (4)†	10.4 ±7.3 (5)*	7.5 ±4.1 (8)

The figures in parentheses indicate the number of segments in each category.
* Probability (P) <0.005 compared with normal values.
† P <0.05 compared with hypokinetic segment.

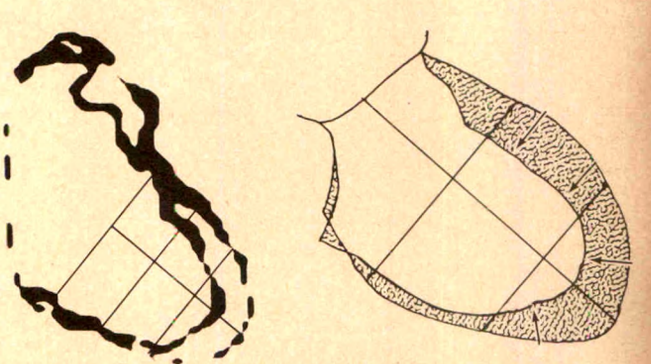


FIGURE 5. Comparison of radionuclide angiographic end-diastolic and end-systolic perimeters in the right anterior oblique view with contrast ventriculographic wall motion analysis. Inferior wall asynergy is depicted by both techniques.

Assessment of the severity of asynergy with contrast ventriculography and radionuclide angiography was also closely correlated (Table II). In 11 areas with anterior asynergy on contrast ventriculography, radionuclide angiography revealed a significant reduction in percent shortening. Akinetic and dyskinetic areas on contrast ventriculography also demonstrated more severe asynergy on radionuclide angiography. Similarly, apical areas appearing akinetic or dyskinetic on contrast ventriculography also demonstrated a marked reduction in segmental shortening (Fig. 4). Of 17 inferior asynergic areas, 13 manifested a significant reduction in wall motion on radionuclide angiography. An example of inferior wall asynergy is shown in Figure 5.

Left versus right anterior oblique radionuclide angiographic ejection fraction: Temporal separation

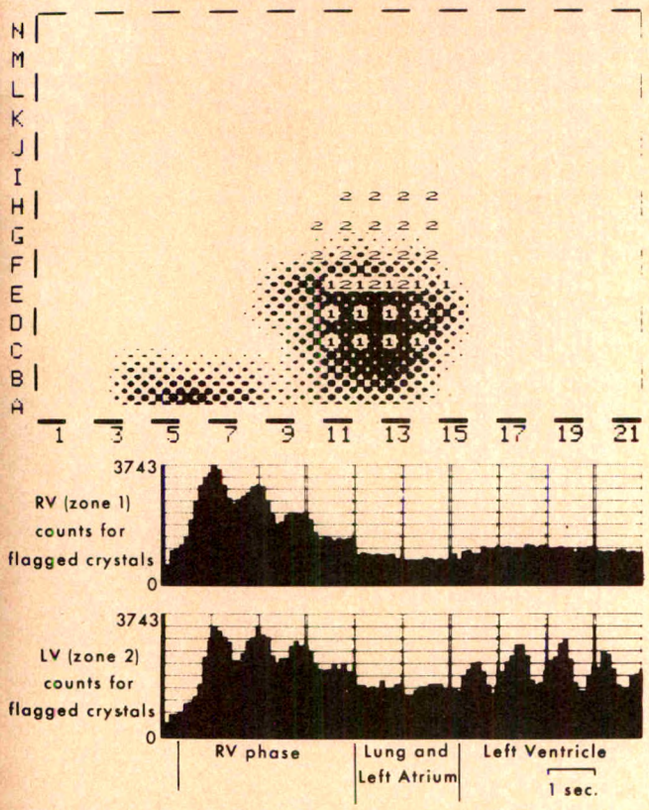


FIGURE 6. Upper panel, zone grid with the right ventricle (RV) flagged as zone 1. The left ventricle (LV) is flagged as zone 2 on the basis of a frame derived from the left ventricular phase. Note the spatial overlap of the two ventricles. As depicted in the time-activity histogram for the right ventricle below the zone grid, there is a rapid initial rise in radioactivity counts as the isotope passes through the right ventricular phase. This is followed by a plateau phase as the bolus dose leaves the right ventricle and enters the lung and left atrium. A similar pattern is seen for the left ventricle (zone 2) which, because of spatial overlap, "sees" the isotope pass through the right ventricle. Again, the plateau phase is seen. However, in the case of zone 2, it is followed by a distinct phasic rise in counts representing arrival of the isotope in the left ventricle.

of right and left ventricular phases was seen in all patients (Fig. 6). Determination of the most appropriate background subtraction for radionuclide angiography in the right anterior oblique view indicated that 35 percent subtraction resulted in the best correlation between the right and left anterior oblique views (Table III). With use of this factor, average ejection fraction as determined with radionuclide angiography was similar for all three groups of patients using either right or left anterior oblique views. Moreover, there was a good correlation ($r = 0.839$) between the left and right anterior oblique views, the regression equation closely parallel with the line of identity (Fig. 7). In addition, results did not differ whether the right (17 patients) or the left (27 patients) anterior oblique view (Fig. 7) was obtained first. Correlation coefficients were 0.839 and 0.840, respectively, for these two sequences.

Right anterior oblique ejection fraction—radionuclide angiography versus contrast ventriculography: Figure 8 shows a correlation coefficient of

TABLE III

Comparison of Ejection Fraction As Determined With Radionuclide Angiography in the Left (LAO) and Right (RAO) Anterior Oblique Projections

	Radionuclide Angiography	
	LAO	RAO
Normal	0.53 ± 0.04	0.54 ± 0.04
CAD	0.58 ± 0.11	0.58 ± 0.18
CAD with asynergy	0.41 ± 0.02	0.41 ± 0.02

CAD = coronary artery disease.

0.824 for ejection fraction determined with radionuclide angiography in the left anterior oblique view compared with the right anterior oblique contrast ventriculogram. A good correlation was observed, although radionuclide angiography tended to underestimate ejection fraction in the case of normally contracting ventricles.

Figure 9 shows a good relation between the ejection fraction determined from radionuclide angiography in the right anterior oblique view after background subtraction and the ejection fraction determined from contrast ventriculography. Similar to the left anterior oblique view, there was a slight tendency for radionuclide angiography to underestimate ejection fraction in hearts with normally contracting ventricles.

Discussion

Accurate delineation of the site, extent and severity of asynergy are of considerable importance in the clinical management of patients with coronary artery disease. Previous studies[18,19] have indicated that anterior or apical asynergy, or both, is associated with greater degrees of hemodynamic dysfunction than inferior asynergy. In addition, selection of patients for aneurysmectomy is based on both the site and the diffuseness of the contractile abnormality defined.[20] Localized anteroapical aneurysms with an adequate residual amount of contractile left ventricular myocardium are considerably more amenable to aneurysmectomy than those located inferiorly, whereas a diffusely asynergic left ventricle does not lend itself to a surgical approach. In addition, anteroapical asynergy is associated with a greater incidence of hemodynamic abnormality than inferior asynergy,[19] and patients with a diffusely asynergic left ventricle have the poorest prognosis.[1]

Comparison of radionuclide angiography and contrast ventriculography: Our study clearly shows that first pass radionuclide angiography in the right anterior oblique projection yields an accurate assessment of the presence, location and severity of asynergic areas of the left ventricle. All of the patients with normal contrast ventriculograms had comparable normal radionuclide angiograms. Of 17 anterior and apical asynergic areas depicted on contrast ventriculography, 16 were localized similarly on radionuclide angiographic study (Table I, Fig. 4). Of particular significance was the ability of the first pass study not only to delineate clearly the apical area but also to differentiate it from the high and mid anterior wall in the right anterior oblique view (Fig. 4). In the 17 cases in which contrast

ventriculograms exhibited asynergy of the inferior wall, the radionuclide angiographic studies demonstrated correspondingly clear inferior contraction abnormalities in 13 (Table I, Fig. 5). Although the reason for the disparity in the remaining four cases is conjectural, one possibility is potential interference of the posterior papillary muscle and the mitral valve apparatus in definition of the inferior wall. A more vertical heart with loss of a good tangential view with or without minor differences in the degree of rotation of the contrast ventriculographic and radionuclide angiographic studies is another possibility.

Significance of asynergy demonstrated with radionuclide angiography: The severity of asynergy bears a close relation to the histopathologic character of the myocardium.[23] Asynergic segments that are hy-

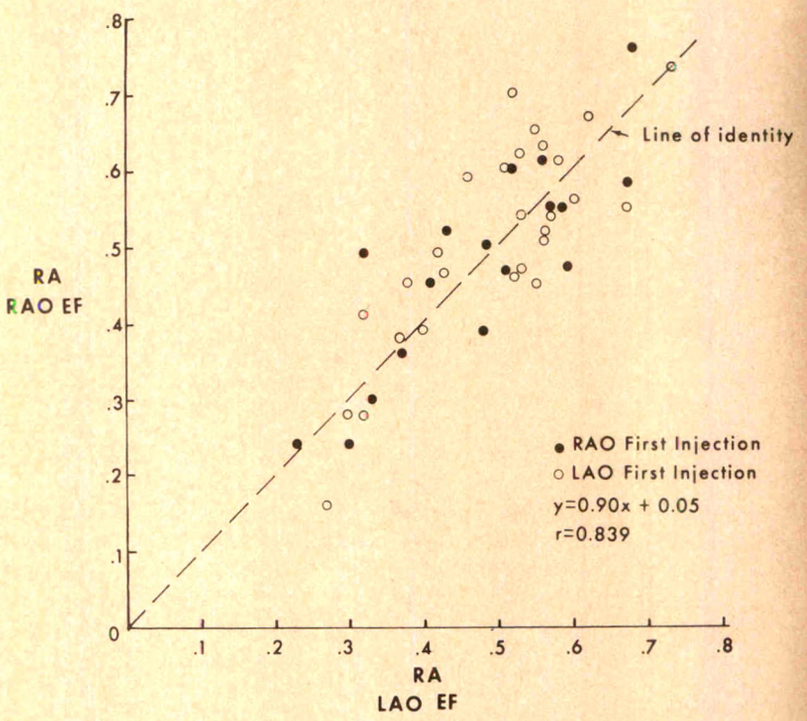


FIGURE 7. Correlation of ejection fraction (EF) determined with radionuclide angiography (RA) in the right (RAO) and left (LAO) anterior oblique views. **Open circles** indicate first injection in left anterior oblique projection; **closed circles** indicate first injection in right anterior projection.

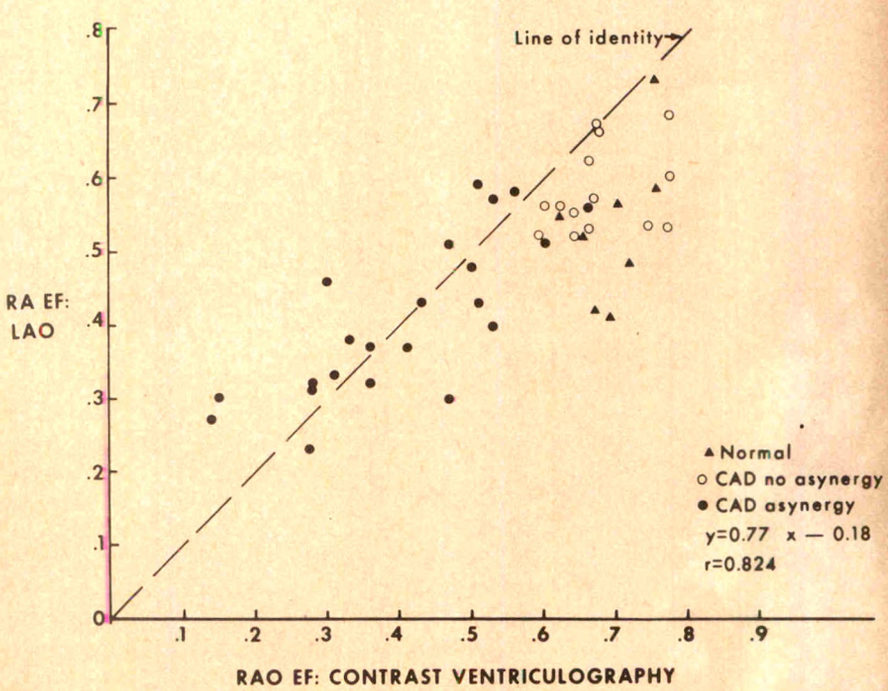


FIGURE 8. Correlation of ejection fraction (EF) assessed with radionuclide angiography (RA) in left anterior oblique (LAO) view with contrast ventriculographic ejection fraction. CAD = coronary artery disease.

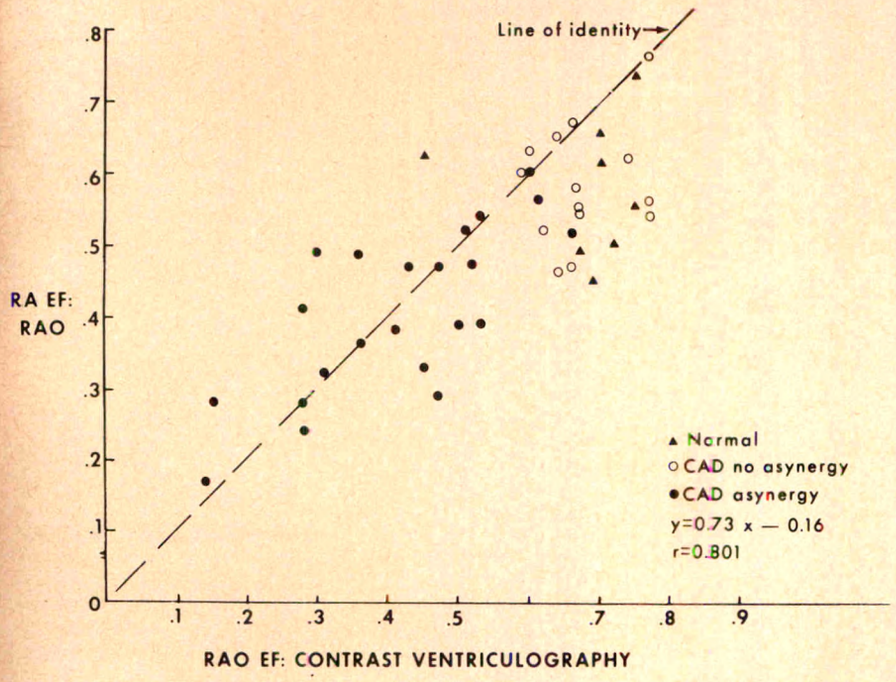


FIGURE 9. Correlation of ejection fraction (EF) determined with radionuclide angiography (RA) in right anterior oblique (RAO) view with ejection fraction obtained with contrast ventriculography.

pokinetic tend to have anatomically normal myocardium whereas those demonstrating akinesia or dyskinesia generally show considerable replacement of myocardium with fibrous tissue.[21] This determination is therefore critically important in assessing both the risks and the benefits of coronary bypass surgery. In addition, Bruschke et al.[1] clearly showed that the medical prognosis of patients with coronary artery disease and asynergy is importantly affected by the severity of a localized contraction abnormality. Our results indicate that first pass radionuclide angiography provides an accurate indication of the severity of asynergy. Akinetic and dyskinetic zones demonstrated a distinctly greater reduction than hypokinetic zones in percent shortening (Table II).

Accuracy of ejection fraction determined with radionuclide angiography in right anterior oblique view: A frequently utilized method of determining ejection fraction using radionuclide angiography has depended on application of standard angiographic area-length formulas based on a geometric model.[6–8] Another methodologic approach intrinsic to radionuclide angiography involves determining ejection fraction on the basis of change in counts from end-diastole to end-systole.[10–12] However, an important consideration in this method is an accurate assessment of the contribution of background so that the ejection fraction is based solely on left ventricular counts.[9] A recent preliminary report by Marshall et al.[22] showed an excellent correlation between ejection fraction determined from radionuclide angiography in the left anterior oblique and anteroposterior views and contrast angiography. Use of the left anterior oblique view is advantageous in this regard because background in this projection is largely limited to the lung and left atrium, thus permitting a more accurate determination of background based on frames that contain these chambers but immediately precede arrival of isotope in the left ventricle. Such a frame or frames can be chosen with the aid of a time-activity curve as well as a serial display that permits examination of the progress of the bolus on a frame by frame basis. Indeed, as seen in Figure 8, ejection fraction in the left anterior oblique view did correlate well with contrast angiographic determination of ejection fraction.

Because determination of ejection fraction based on a difference in counts from diastole to systole is independent of geometry, ejection fraction for the same patient under similar conditions should be identical regardless of projection. Thus, the right anterior oblique view could be standardized, provided that the correction chosen for background was consistent over a wide range of patients, left ventricular function and sequence of injections. Indeed, as seen in Table III and Figure 7, it was found that background subtraction of 35 percent combined with the three peak method resulted in excellent correlation of radionuclide angiographic ejection fraction determined in the right anterior oblique view with ejection fraction determined in the left anterior oblique projection. Moreover, this same background subtraction applied equally well over a wide range of ejection fraction for normal as well as abnormal segmental or diffuse left ventricular contraction and was unaffected by the sequence of right and left anterior oblique injections. However, some underestimation of ejection fraction by the radionuclide angiography occurred in the normal range.[23]

Clinical implications: Potential limitations of radionuclide angiography do exist based on current technology. Although a framing rate of 20 to 25/sec is

considered adequate,[24] higher frame rates would clearly enhance delineation of wall motion and aid in detection of more subtle changes. In addition, although higher count rates would clearly improve detail, the counts obtained in the study were within acceptable limits[9] and are capable of providing good delineation of end-diastolic and end-systolic edges.[25]

Thus, radionuclide angiography performed in the right anterior oblique view using first pass techniques permits an accurate assessment of the wall motion of areas of left ventricle suboptimally seen in either the left anterior oblique or anteroposterior views. In addition, determination of ejection fraction is possible in this view, further adding to the utility of this projection.

Acknowledgment

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Estimation of Left Ventricular Volumes in Man From Biplane Cineangiograms Filmed in Oblique Projections

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In patients with coronary artery disease, right and left anterior oblique views of the left ventricle are considered optimal for assessment of regional wall motion, but the accuracy of ventricular volumes determined from these projections has not been validated. Eleven postmortem left ventricular casts were filmed with the 35 mm cine technique in the 30° right anterior oblique and 60° left anterior oblique positions, and volumes were calculated using the area-length method. True volume, assessed from volume displacement, ranged from 15 to 185 cc. Calculated volume ($V_{oblique}$) slightly but consistently overestimated true volume (V_T), with close correlation and a small standard error of the estimate (SEE): $V_T = 0.989\ V_{oblique} - 8.1$ cc, $r = 0.99$, SEE = 8 cc. With use of this regression equation, values for left ventricular volumes and ejection fraction were calculated from biplane oblique (30° right anterior oblique/60° left anterior oblique) cineangiograms in 17 normal adults. Values for end-diastolic volume index (72 ± 15 cc/m² [mean ± standard deviation]), end-systolic volume index (20 ± 8 cc/m²), stroke volume index (51 ± 10 cc/m²) and ejection fraction (0.72 ± 0.08) were similar to those reported by others. Examination of the effects of variable obliquity suggests that strict standardization of the degree of obliquity is necessary to offset variation in the long axis in the left anterior oblique projection caused by foreshortening.

Measurement of ventricular volume has become a standard technique in assessing left ventricular function.[1–6] As recently reviewed by Rackley,[1] one of the most widely utilized approaches to the measurement of left ventricular volume is the area-length method introduced by Dodge et al.[7] This method assumes that the left ventricle can be represented by a three dimensional ellipsoid reference figure and that the dimensions of this figure can be determined from angiograms taken in perpendicular planes. In this method, anteroposterior (AP) and lateral (LAT) projections of the left ventricular silhouette are used to compute volume, using the formula $V = (\pi/6)L \cdot D_{AP} \cdot D_{LAT}$. Long axes in both planes (LAT) are directly measured; minor axes (D) are calculated from the area (A) of each silhouette, determined with planimetry, and its respective long axis using the formula $D = 4A/\pi L$.

In patients with ischemic heart disease, right and left anterior oblique views of the left ventricle have been considered optimal projections for assessing regional abnormalities of wall motion.[8,9] Although studies have been reported validating the use of the area-length method for biplane anteroposterior and lateral left ventriculography[5,7] as well as single plane ventriculography,[3,10,11] neither the validity of this method nor its appropriate regression equation has been reported for biplane right and left anterior oblique ventriculography. In this communication we describe such a study using biplane right and left anterior oblique cineventriculograms of left ventricular casts from 11 specimens of postmortem hearts from patients without heart disease and of 17 hearts in a series of normal living subjects.

From the Departments of Medicine and Radiology, Peter Bent Brigham Hospital and Harvard Medical School, Boston, Massachusetts. This study was supported in part by U. S. Public Health Service Grants HL 19246-01 and HL 07049-02 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received July 25, 1977; revised manuscript received November 9, 1977, accepted November 9, 1977.

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Material and Methods

Normal subjects: Seventeen patients who had undergone cardiac catheterization at the Peter Bent Brigham Hospital and had no hemodynamic or angiographic evidence of cardiac disease formed the normal population. Simultaneous biplane right and left anterior oblique cineventriculography was performed using horizontal and vertical Siemens cesium iodide image intensifiers with the patients rotated to a 30° right anterior oblique projection in a Spectrum cradle. Left ventricular opacification was achieved by injecting 30 to 50 cc of radiopaque contrast material (Renografin 76®) at a rate of 12 to 15 cc/sec through no. 7 or 8 French multiple side hole catheters. Filming was performed at 60 frames/sec in both planes using 35 mm Arriflex cameras and Kodak CFR cine film. Tracings of end-diastolic and end-systolic left ventricular silhouettes allowed measurement of long axes (L, the longest measured chord in any direction within the ventricular silhouette) and area (A) of each silhouette in both right and left anterior oblique projections (Fig. 1). From these data, minor axis (D) was calculated for each silhouette as $D = 4A/\pi L$.

Left ventricular casts: Eleven left ventricular casts were made from fresh (obtained less than 24 hours after death) postmortem specimens of human hearts, using Dow Corning 3110 RTV Encapsulant mixed with barium sulfate powder (Fig. 2). No heart was judged to exhibit rigor mortis by our cardiac pathologist (Dr. Michael Fishbein). The encapsulant material is certified to exhibit no significant change in shape or dimensions (linear shrinkage less than 0.35 percent) as it solidifies from its initially liquid form. The hearts were carefully washed free of blood clots, the mitral valve sewn closed and the encapsulant slowly infused through a plastic catheter inserted through the aortic valve.

The filling of the ventricle by the cast material was passive, and the material was not injected under positive pressure. After the casts had hardened (more than 12 hours) the left ventricular free wall was incised and the ventricle carefully peeled off the hardened cast by blunt dissection. The hearts used were from children and adults free of obvious disease detectable on gross examination at the autopsy table, and the specimens were chosen to represent a wide range of sizes. True volume was determined by submersion of each cast (suspended with ultralight fishing line) in water and measurement of the displaced volume. Care was taken to exclude air bubbles trapped in the interstices of the casts. True volumes represented an average of at least six measurements for each cast.

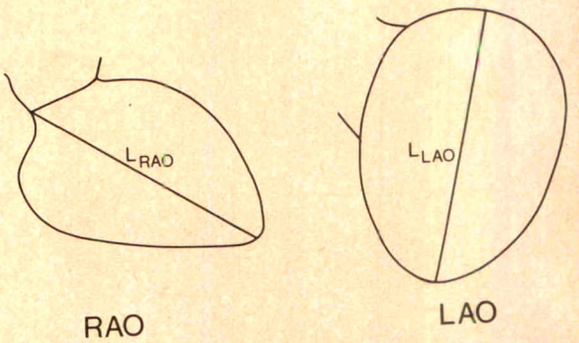


FIGURE 1. Diastolic left ventricular silhouettes of right anterior (RAO) and left anterior oblique (LAO) cineangiograms. The long axis (L) is the longest chord in each view that can be fitted within the confines of the silhouette. There is no need for specific orientation of the long axis.

The casts were filmed using the same radiologic equipment and filming techniques as in the patient studies. Each cast was positioned in the biplane field to approximate the relations of septum, anterior wall and apex found during left ventriculography in man. To ensure the proper degree of rotation about the transverse axis of the heart, the ratio of the long axis in the left anterior oblique projection (L_{LAO}) to that in the right anterior oblique projection (L_{RAO}) was determined for

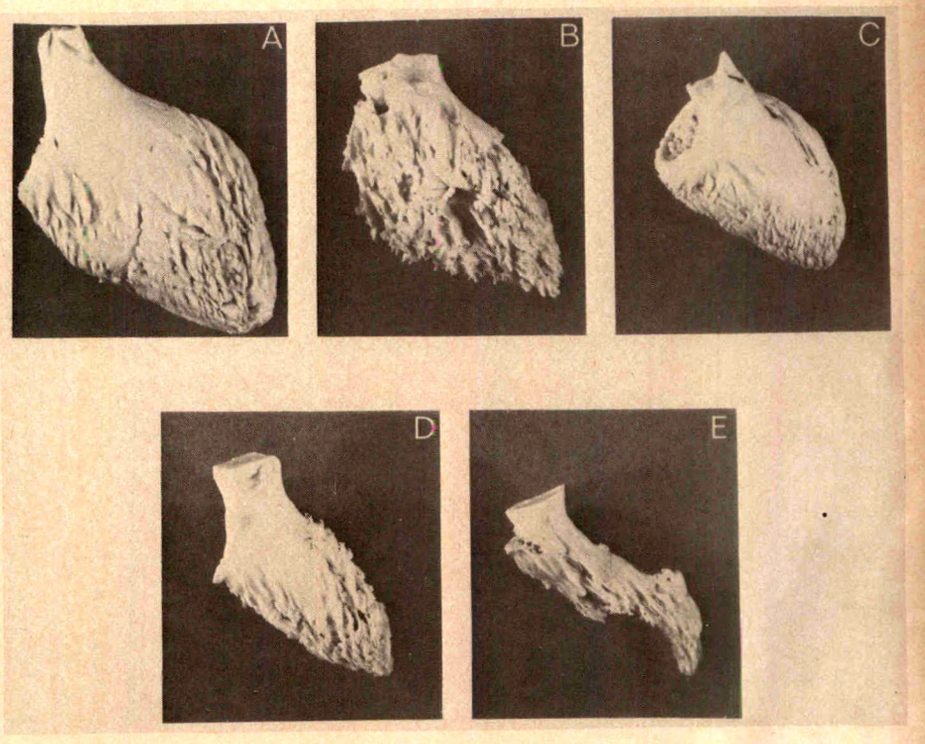


FIGURE 2. Photographs of 5 of the 11 human left ventricular casts from this study, illustrating the range in size and configuration utilized.

TABLE I

Areas, Long Axes, Calculated Volumes and True Volumes for 11 Human Left Ventricular Casts

Cast	A_{RAO} (cm^2)	A_{LAO} (cm^2)	L_{RAO} (cm)	L_{LAO} (cm)	V_{true} (cm^3)	$V_{oblique}$ (cm^3)	V_{RAO} (cm^3)
1	13.4	11.8	8.0	6.4	15	21	19
2	18.5	15.1	8.3	6.4	25	37	35
3	16.5	11.2	6.8	4.9	29	32	34
4	20.6	15.6	7.2	5.7	37	48	50
5	25.2	19.1	7.3	6.2	66	66	74
6	29.7	19.6	8.7	6.1	74	81	86
7	32.6	24.4	9.4	6.5	79	104	96
8	34.8	30.3	9.0	7.4	110	121	114
9	40.3	28.9	8.9	6.6	137	150	155
10	44.5	31.5	9.8	7.3	146	163	172
11	48.0	30.3	10.1	6.9	185	179	194

A_{LAO} and A_{RAO} = area in left and right anterior oblique projections, respectively; L_{LAO} and L_{RAO} = long axis in left and right anterior oblique projections, respectively; $V_{oblique}$ = biplane oblique volume, as defined in Equation 1, Methods; V_{RAO} = volume in right anterior oblique, as defined in Equation 3, Methods; V_{true} = true volume.

the 17 normal human subjects, and was found to be $L_{LAO}/L_{RAO} = 0.76 \pm 0.09$ (mean ± standard deviation). Each cast was slowly rotated in the biplane field until fluoroscopic images of the paired silhouettes gave an L_{LAO}/L_{RAO} ratio equal to that for the human subjects. The casts were then fixed in this position and filmed. A single cast was filmed in multiple projections with various degrees of obliquity.

Methods of volume determinations: Volume calculation for the filmed silhouettes of ventricular casts were carried out using three methods. First, long axes (L_{RAO} and L_{LAO}) were directly determined as the longest measured axes within each silhouette (Fig. 1), areas (A_{RAO} and A_{LAO}) were assessed by planimetry for each pair of silhouettes, and volumes were calculated by the area-length method:

$$V_{oblique} = \frac{\pi}{6} L_{max} \left\{\frac{4A_{RAO}}{\pi L_{RAO}}\right\} \left\{\frac{4A_{LAO}}{\pi L_{LAO}}\right\} = \frac{8}{3\pi} \cdot \frac{A_{RAO}A_{LAO}}{L_{min}} \quad (1)$$

where $V_{oblique}$ is the *calculated* volume from right and left anterior oblique views, and L_{max} and L_{min} are the larger and smaller, respectively, of L_{RAO} and L_{LAO}. Areas and lengths were corrected for magnification by use of a calibrated grid (NAMIC Area Determination Grid, North American Instrument Corporation, Hudson Falls, New York) of known dimensions filmed at the level of the casts or, for the patient studies, at the level of the left ventricle.[6,11,12] The grid consists

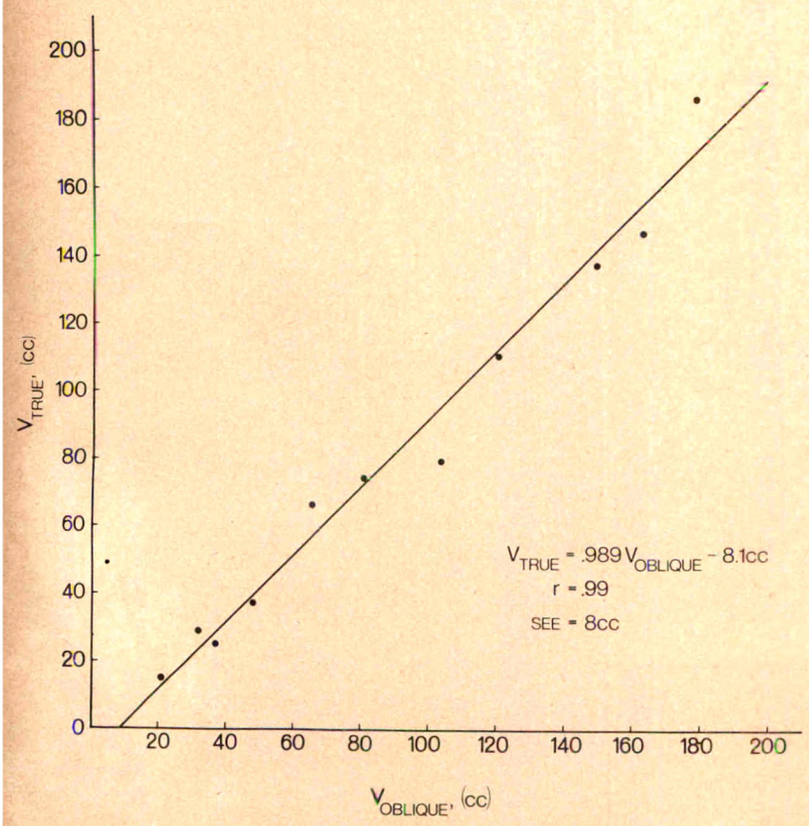


FIGURE 3. Regression analysis for 11 human left ventricular casts of true volume (V_{TRUE}) versus volume calculated from biplane oblique cine films of each cast ($V_{OBLIQUE}$) using Equation 1, Methods. As can be seen, $V_{OBLIQUE}$ slightly overestimated V_{TRUE} although the correlation was excellent. The regression equation (**lower right**) permits correction for this overestimation. r = correlation coefficient; SEE = standard error of the estimate.

of multiple squares with 1.0 cm edges of lead laminated in plexiglass. The grid is positioned so that it is centered in each fluoroscopic field and filmed by each camera. The X-ray tubes are in the same position for filming of the ventricle (or of the casts) as for filming of the grid, thus ensuring that the position of the grid in space and its relative distance from the X-ray equipment is identical to that of the patient's left ventricle or of the ventricular cast. By subsequently measuring the apparent size of the grid squares when viewing the films, one can correct measured lengths and areas for magnification by multiplying by a correction factor (CF):

$$CF = \sqrt{A_T/A_M} \quad (2)$$

where A_T = true area of grid squares and A_M = measured area of grid squares.

Second, the area product method, first utilized by Chapman et al.[13] in 1958 and subsequently by Dodge et al.,[7] was used. This approach is based upon the empiric observation[13] that the logarithm of the product of the areas in perpendicular planes ($X = A_{RAO}A_{LAO}$) is closely correlated with the true volume (V_{true}):

$$Log_e V_{true} = m Log_e X + B \quad (3)$$

where m and B are constants. Third, we analyzed only the right anterior oblique silhouette for each cast, and calculated a volume based on the assumption of symmetry around the minor axis, as previously reported by Dodge et al.[2]:

$$V_{RAO} = \frac{\pi}{6} \cdot L_{RAO} \left\{\frac{4A_{RAO}}{\pi L_{RAO}}\right\} \left\{\frac{4A_{RAO}}{\pi L_{RAO}}\right\} = \frac{8A^2_{RAO}}{3\pi L_{RAO}} \quad (4)$$

where V_{RAO} is the *calculated* volume from right anterior oblique area and length alone. All lengths, areas and calculated volumes were corrected for magnification using the calibrated grid system.

Calculated volumes were compared with true volumes by linear regression analysis and the coefficient of correlation (r) and standard error of the estimate used as tests of validity of the methods.

For the patient studies, left ventricular volumes were calculated from the measured biplane silhouettes according to the area-length method by Equation 1, and then regressed to true volume measurements using the regression equation derived from the cast studies. The volumes are expressed in cubic centimeters per square meter of body surface area (using the formula of Dubois and Dubois[14]) to allow comparison with values in normal subjects previously reported by Kennedy et al.[15] and Hammermeister et al.[16] Although ventricular volumes are commonly expressed in terms of body surface area, Holt et al.[17] pointed out that in other mammalian species cardiac output is more precisely a function of body weight than of body surface area. Accordingly, we also reported body weight and body surface area for each subject to permit normalization of the ventricular volumes for body weight.

Results

Left ventricular casts: Areas, long axes, calculated volumes and true volumes for each cast are given in Table I. Calculated biplane oblique volumes and calculated single plane right anterior oblique volumes regularly exceeded true volumes. Photographs of representative left ventricular casts in Figure 2 demonstrate the range in size and configuration of the casts.

Regression analyses of calculated versus true volumes for biplane oblique as well as single plane right anterior oblique formulas are given in Figures 3 and 4, respectively. As is evident, the validity of both methods is supported reasonably well by the high coefficients of correlation and the small standard errors of the esti-

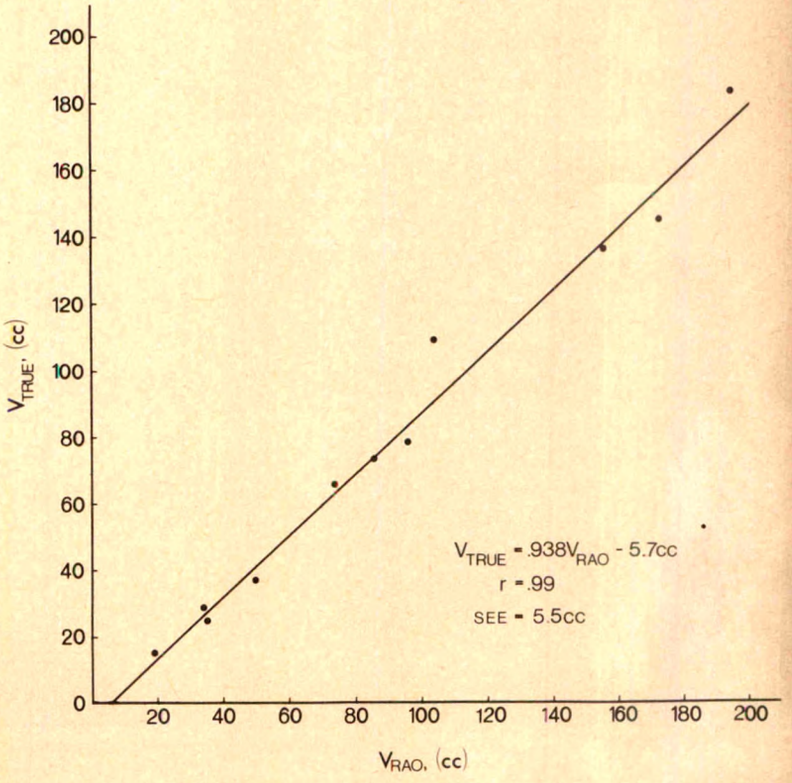


FIGURE 4. Regression analysis for 11 human left ventricular casts of true volume (V_{TRUE}) versus volume calculated from single plane 30° right anterior oblique cineangiographic films of each cast (V_{RAO}) using Equation 4, Methods. There is overestimation of V_{TRUE} by V_{RAO}, although the correlation is high and standard error of the estimate is small. The regression equation permits correction for the overestimation.

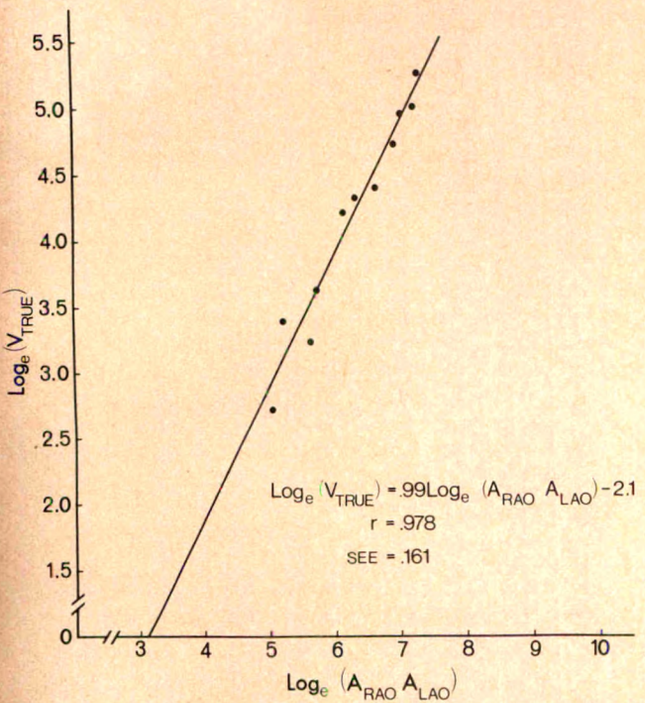


FIGURE 5. Regression analysis of the logarithm of true ventricular volume (Log_eV_{TRUE}) plotted against the logarithm of the product of right and left anterior oblique silhouette area ($Log_eA_{RAO}A_{LAO}$) for 11 human left ventricular casts. See text for discussion.

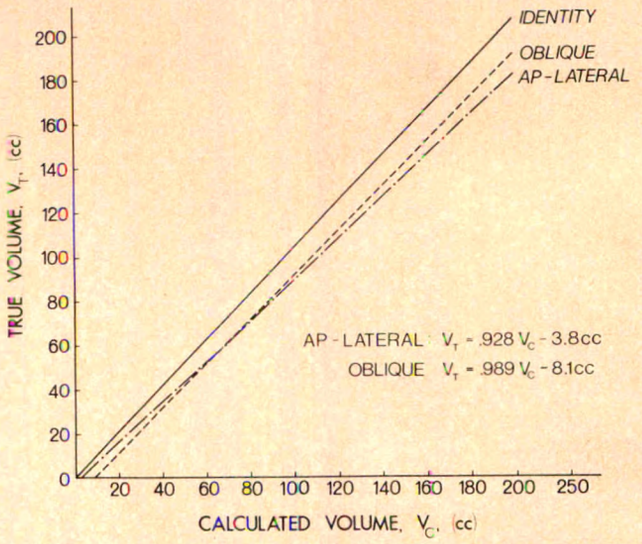


FIGURE 6. Comparison of the regression equation reported by Dodge et al.[7] for the biplane anteroposterior and lateral large film technique (AP-LATERAL) and the regression equation from the present study for biplane oblique 30° right anterior oblique, 60° left anterior oblique cineventriculography (OBLIQUE). Both methods overestimate true volume to a similar extent. See text for discussion.

mate. The regression equation relating true volume of the casts and volume calculated from the biplane oblique (30° right anterior oblique/60° left anterior oblique) cineventriculographic film pairs by the area-length method is $V_{true} = 0.989\ V_{oblique} - 8.1$ cc. Similarly, the relation between true volume and volume calculated from the single plane 30° right anterior oblique cineventriculogram is $V_{true} = 0.938\ V_{RAO} - 5.7$ cc.

The area product method is illustrated in Figure 5, where the logarithm of true ventricular cast volume is plotted against the logarithm of the product of right and left anterior oblique silhouette areas. The coefficient of correlation of this empirical method is surprisingly high, and the standard error of the estimate quite small.

In a single cast, volumes were calculated from multiple film pairs representing a range of degrees of obliquity from 0° to 40° in the right anterior oblique projection (90° to 50° left anterior oblique projection). There was a 23 percent variation in the long axis of the left anterior oblique projection due to variable foreshortening and a 25 percent variation in the calculated volume. The long axis in the left anterior oblique projection also could be altered by the degree of forward tilt of the apex.

Normal subjects: Values for left ventricular volumes, dimension and ejection fractions in 17 normal subjects are listed in Table II. The volumes, calculated from biplane oblique cineangiograms (30° right anterior oblique/60° left anterior oblique) and the regression equation derived from Figure 3 ($V_{true} = 0.989\ V_{oblique} - 08.1$ cc), are listed in Table II. Table III compares the values found in this study with those previously reported by others[15,16] using different techniques. There is substantial similarity in the results of the three studies.

Discussion

Despite the routine use of biplane oblique (right and left anterior oblique) left ventriculography in many laboratories, validation of this technique as a reliable method for calculating left ventricular volumes has not been reported. In this study, we demonstrated remarkably good correlation ($r > 0.95$) between true ventricular volumes and those calculated from biplane oblique cineangiograms. Furthermore, using this methodology, absolute values for left ventricular volumes were calculated in 17 normal subjects and found to be substantially similar to normal values reported from other laboratories[15,16] using different methods (Table III).

True versus calculated ventricular volumes: Importance of rotation: The precise relation between true (V_{true}) and calculated ($V_{oblique}$) volumes using the biplane oblique method was given by $V_{true} = 0.989\ V_{oblique} - 8.1$ cc (Fig. 6). This indicates overestimation of true volume by the oblique cineangiographic method. Overestimation of true volume was also reported by Dodge et al.,[7] who found that for the anteroposterior-lateral biplane method, $V_{true} = 0.928\ V_{calculated} - 3.8$ cc (Fig. 6). As Dodge et al.[7] observed, angiographic estimates of ventricular volume in general overestimate true

TABLE II

Left Ventricular Volumes,* Dimensions and Ejection Fractions Calculated From Biplane Oblique Cineangiograms in 17 Normal Subjects

	Age (yr) & Sex	Weight (kg)	BSA (m^2)	EDVI (cc/m^2)	ESVI (cc/m^2)	SVI (cc/m^2)	EF	LAO		RAO	
								D_{ED}	L_{ED}	D_{ED}	L_{ED}
1	35 F	56.8	1.55	69	21	48	0.70	4.9	6.8	5.2	8.9
2	54 M	80.8	1.90	67	12	55	0.82	5.5	6.9	5.2	9.8
3	38 M	73.6	1.94	71	29	42	0.59	5.2	7.8	6.2	9.1
4	49 F	53.6	1.49	92	32	60	0.65	5.2	7.6	5.5	8.3
5	48 M	78.6	1.95	52	8	44	0.85	5.0	5.6	5.1	8.9
6	50 M	68.2	1.78	73	29	44	0.60	5.2	7.8	5.5	8.3
7	55 M	81.8	2.02	60	14	46	0.77	5.9	7.6	5.2	8.6
8	42 F	67.3	1.68	64	22	42	0.66	5.0	6.6	5.2	9.5
9	43 M	113.6	2.40	90	22	68	0.76	5.8	8.4	7.1	11.0
10	42 M	62.3	1.70	86	23	63	0.73	5.0	6.4	5.7	11.0
11	58 M	75.0	1.91	92	33	59	0.64	5.6	7.0	5.3	9.0
12	49 F	65.9	1.74	46	14	32	0.70	5.0	5.6	4.6	8.1
13	36 M	67.3	1.76	90	22	68	0.76	5.6	7.6	5.6	10.1
14	37 M	83.6	1.95	83	21	62	0.75	5.5	7.6	5.9	10.3
15	41 F	56.4	1.52	60	10	50	0.83	4.2	6.4	5.2	9.2
16	59 M	76.4	1.96	60	15	45	0.75	5.3	8.0	5.3	9.2
17	34 M	93.2	2.16	75	20	45	0.60	6.0	7.7	5.9	9.9
Mean				72	20	51	0.72	5.3	7.1	5.5	9.4
± SD				± 15	± 8	± 10	± 0.08	± 0.4	± 0.8	± 0.6	± 0.9

* Volumes were calculated by the area-length method (Equation 1, Methods) and regressed to true volume by the formula $V_{true} = 0.989\ V_{oblique} - 8.1$ cc (Fig. 3).

BSA = body surface area; D_{ED} = end-diastolic diameter; EDVI = left ventricular end-diastolic volume index; EF = ejection fraction; ESVI = left ventricular end-systolic volume index; LAO = left anterior oblique; L_{ED} = end-diastolic long axis; RAO = right anterior oblique; SVI = left ventricular stroke volume index.

volume, and this is probably partly caused by the portion of the ventricular chamber occupied by papillary muscles and trabeculae carnae as well as the inadequacy of the ellipsoid reference figure in describing a chamber with irregular shape and margins.

The similarity between the regression data of Dodge et al. and our data might suggest relative unimportance of the degree of obliquity in determining true volume. However, study of multiple film pairs of a cast taken at various degrees of obliquity indicates that there may be substantial variation in calculated volume with rotation. This is probably due to foreshortening in the left anterior oblique projection, with progressive diminution in the long axis, which almost always constitutes the minimal long axis. As Equation 1 indicates, a decrease in the minimal long axis (L_{min}) due to such foreshortening can be expected to increase calculated volume, thus potentially increasing the overestimation of true volume inherent in the angiographic method. For this reason, we consider it important to pay careful attention to maintaining a constant and reproducible degree of obliquity (30° right and 60° left anterior oblique) if a single regression equation is used to estimate true volume.

As previously observed,[7,13] the logarithm of the area product in each obliquity ($A_{RAO}A_{LAO}$) correlated quite well with the logarithm of true volume. There appears to be no complex theoretic explanation for this observation, which probably reflects the preponderant influence of the area product and the narrow variation of the minimal long axis (L_{min}) in Equation 1.

Single plane left ventricular cineangiograms were

TABLE III

Values for Left Ventricular Volumes in Normal Adults

	Present Study	Kennedy et al.[15]	Hammer-meister et al.[16]
EDVI (cc/m^2)	72 ± 15	70 ± 20	78 ± 15
ESVI (cc/m^2)	20 ± 8	24 ± 10	. . .
SVI (cc/m^2)	51 ± 10	45 ± 13	50 ± 13
Ejection fraction	0.72 ± 0.08	0.67 ± 0.08	0.64 ± 0.07
Age range (yr)	34–59; mean 45	16–64	mean 35
Male/female ratio	12/5	11/5	. . .
Angiographic techniques	Biplane oblique projections	Biplane AP & lateral projections	Single plane RAO or AP projections

All volumes are expressed as mean ± standard deviation.
AP = anteroposterior; other abbreviations as in Table II.

reported by others to give reliable estimation of left ventricular volumes, but validation of this reliability generally utilized as the reference standard a biplane volume calculation (rather than true volume as assessed from ventricular casts).[10,11] We found a close correlation between single plane right anterior oblique left ventricular volume calculation in the normal heart and true volume ($V_{true} = 0.938\ V_{RAO} - 5.7$ cc). This indicates that left ventricular volume calculated from the single plane right anterior oblique projection also overestimates true volume, and the overestimation is greater than that seen using the biplane oblique volume method.

Implication: This study has validated the use of biplane oblique left ventriculography as a method of assessing true left ventricular volume. Standardization of the degree of obliquity (30° right and 60° left anterior oblique) is required if the particular regression equation found to apply in this study is to be utilized.

Acknowledgment

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Modification of Intraaortic Balloon Catheter to Permit Introduction by Cardiac Catheterization Techniques

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Intraaortic balloon counterpulsation has been widely applied for treatment of left ventricular pump failure and intractable angina. However, its use has been limited by the difficulty of balloon insertion in some patients and vascular complications in others. An AVCO intraaortic balloon was modified by the addition of a central lumen to allow pressure monitoring, injection of contrast medium and passage of a guide wire. The device was successfully used in 15 of 16 patients, including 4 of 5 in whom attempts to place a standard balloon catheter had failed. No significant vascular complications occurred in any patient. The modified balloon catheter appears to increase the efficacy and safety of insertion and allows immediate and continuous monitoring of arterial pressure.

Intraaortic balloon counterpulsation has long been known to be effective treatment for left ventricular pump failure after cardiopulmonary bypass.[1,2] Recently, studies have demonstrated its efficacy in the support of patients with cardiogenic shock after acute myocardial infarction,[3,6] as an adjunct to surgery in patients with acute ventricular septal defect or mitral regurgitation[7,8] and in the management of refractory myocardial ischemia.[9]

Although a good record of safety and efficacy has been established, vascular complications associated with balloon placement have been reported. These have included mechanical trauma to sclerotic arteries at the site of balloon insertion,[10] aortic dissection,[4,10–15] ischemia of the catheterized limb[4,10,11,15,16] and false aneurysm of the femoral artery.[1] Less commonly noted, but no less important, has been the inability to accomplish balloon counterpulsation in some patients because the device cannot be advanced past atherosclerotic obstruction in the distal arterial tree.[10,12,14,15,17]

In large measure these difficulties arise because of the need to pass the relatively inflexible balloon catheter blindly through the arterial tree. Its progress is not routinely monitored by any means other than overt resistance to passage. In this study we report our clinical experience with an AVCO intraaortic balloon that was modified to allow pressure monitoring, injection of contrast medium and passage of a guide wire.

Material and Methods

The modified balloon catheter and its passage: The standard AVCO trisegment intraaortic balloon catheter (30 or 40 cc balloon) was modified by the addition of a central lumen (1 mm internal diameter) extending from the tip of the balloon to a plastic connector near its proximal end (Fig. 1 and 2). The patient was given local anesthesia and the device inserted through a Dacron® vascular graft sewn end to side to the common femoral artery in standard fashion. The central lumen was then connected to a fluid-filled system and arterial pressure recorded using a Statham P23db strain gauge and an Electronics for Medicine DR-8 recorder. The balloon catheter was advanced under fluoroscopic control with constant monitoring of the arterial pressure tracing. If, at any time during

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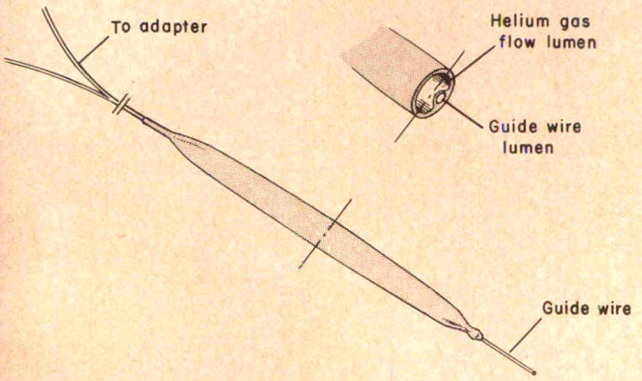


FIGURE 1. Diagrammatic representation of a modified intraaortic balloon.

passage of the catheter, resistance was met or damping of the arterial pressure wave occurred, contrast agent was injected through the central lumen to document the source of the obstruction. If the balloon still could not be passed beyond the obstruction but an arterial lumen could be identified, a Teflon®-coated wire with a flexible tip was passed and manipulated into the descending aorta. The balloon catheter was then carefully advanced over the guide. It was placed with the tip just distal to the origin of the left subclavian artery and the positioning verified by the injection of 10 cc of Renografin-60® through the central lumen.

The modified balloon catheter is as inflexible as the standard catheter, and to pass it over the guide wire, the following approach was necessary: The guide wire was passed to the arch of the aorta to leave a considerable length of wire protruding beyond the catheter tip. The catheter was then carefully advanced under constant fluoroscopic observation. During this maneuver the guide wire was gradually withdrawn to prevent it from entering the head vessels or ascending aorta. Considerable force was occasionally necessary to advance the balloon catheter, particularly if it had to traverse a tortuous course (Fig. 3).

Once in place, inflation and deflation of the balloon were adjusted using the arterial pressure tracing recorded from the balloon tip. Arterial pressure was subsequently monitored using the lumen of the balloon catheter in all patients (Fig. 4). Systemic heparinization was instituted and all patients were carefully observed for signs of limb ischemia or peripheral embolization. A complete blood count, platelet count, determinations of serum electrolytes and blood urea nitrogen and urinalyses were performed daily in all subjects.

Patients: The modified intraaortic balloon was used in 16 patients with a mean age of 58 years (range 36 to 71). There were 10 men and 6 women. The indications for balloon insertion were intermediate coronary syndrome before cardiac catheterization and surgery (12 patients), cardiogenic shock (3 patients) and severe mitral regurgitation with low cardiac output (1 patient).

Results

The modified intraaortic balloon was successfully placed in 15 of the 16 patients in this series, including 4 of 5 in whom prior attempts to place a standard AVCO balloon catheter had failed. Pertinent clinical information and results of balloon placement in the 16 patients are summarized in Table I.

Results after failure with standard intraaortic balloon catheter: Five patients (Cases 2, 4, 9, 11 and 12) had prior unsuccessful attempts to insert the standard AVCO intraaortic balloon catheter. These attempts failed because of severe aortoiliac atheromatous disease. In three of these patients (Cases 2, 4 and 5), catheterization with the modified balloon was initially attempted in the same limb. Injection of contrast agent through the lumen of the modified catheter revealed intimal dissections produced by the standard catheter in the earlier attempt. The contralateral limb was then entered, and in Patients 4 and 5 catheterization was accomplished with the aid of a guide wire despite severe atheromas documented with the contrast agent. In Patient 2 the guide wire could not be advanced to the descending aorta, and the attempt to perform balloon catheterization was abandoned. In the remaining two patients in whom catheterization with the standard balloon failed, catheterization was easily performed with the modified catheter using the contralateral femoral artery. Pressure monitoring alone was required in one patient (Case 11) and a guide wire in the other (Case 12). There were no vascular complications attributable to the modified balloon in this group.

Primary use in patients with suspected peripheral vascular disease: In Cases 6, 8, 10, 14, 15 and 16 the modified balloon was selected for use because the patients had clinical evidence of peripheral vascular disease (bruits or diminished pulses), and it was anticipated that catheterization with a

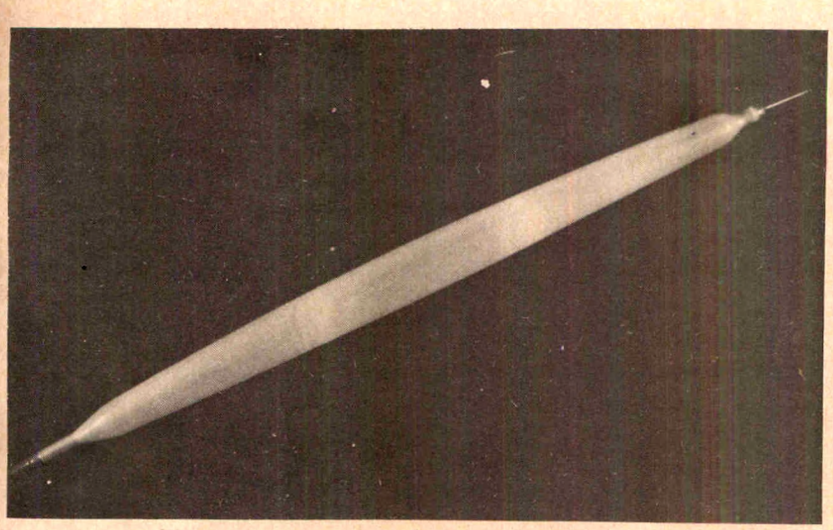


FIGURE 2. Photograph of a modified intraaortic balloon catheter with the guide wire in place exiting at the tip.

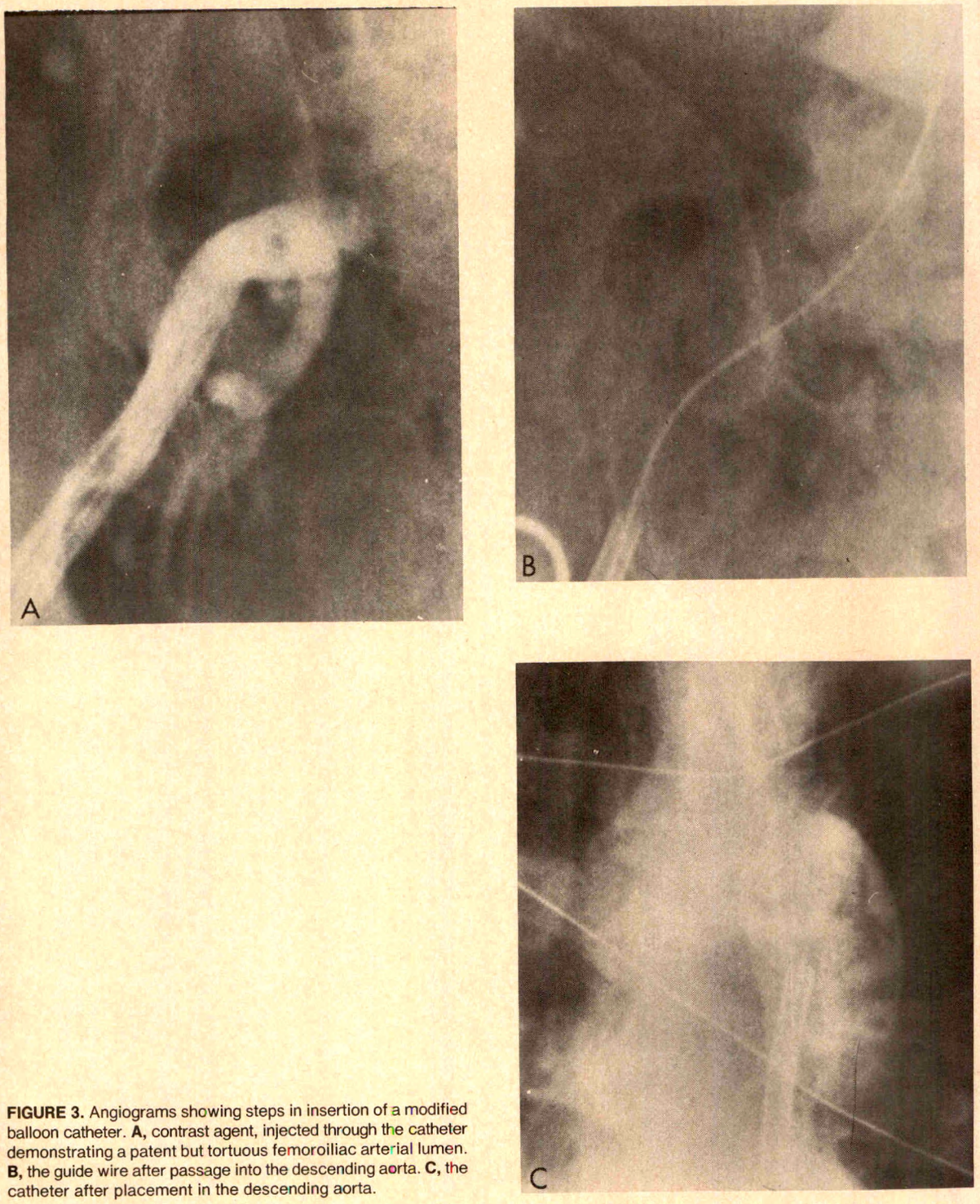


FIGURE 3. Angiograms showing steps in insertion of a modified balloon catheter. **A,** contrast agent, injected through the catheter demonstrating a patent but tortuous femoroiliac arterial lumen. **B,** the guide wire after passage into the descending aorta. **C,** the catheter after placement in the descending aorta.

standard balloon might prove difficult. In all six cases, resistance or pressure damping, or both, occurred, and atheromatous disease and tortuosity in the femoral and iliac vessels was documented with injection of contrast medium. A guide wire was passed to the descending aorta and the balloon was maneuvered over the wire into proper position. In one of these patients (Case 8), the dorsalis pedis pulse was decreased after counterpulsation was instituted, but no signs of limb ischemia were noted. The balloon was removed after bypass surgery with restoration of the dorsalis pedis pulse to its preoperative state. No sequelae have resulted. In Patient 16, some difficulty was experienced in advancing a straight guide wire past the aortic bifurcation. A 15 mm J wire was placed and balloon catheterization then accomplished. In Patient 10, the entire aortoiliac tree was diffusely diseased and heavily calcified. A guide wire was introduced into the descending aorta, but resistance to passage of the balloon still occurred and considerable force was required to advance a 30 cc balloon. Eventually the catheter was successfully placed and counterpulsation begun. The patient experienced transient pallor and dysesthesia of the catheterized limb that resolved entirely within 2 hours without discontinuation of balloon assistance.

Postoperatively, the balloon was removed and the patient has experienced no further ischemic symptoms in the limb. Pulses have returned to the preoperative state.

Primary use in absence of clinical peripheral vascular disease: The modified balloon was used primarily in the remaining five patients (Cases 1, 3, 7, 9 and 13), even though no clinical suggestion of peripheral vascular disease was present. In three patients (Cases and 1, 7 and 13), it was passed easily to the aorta under pressure monitoring using standard technique. In two patients (Cases 3 and 9), the catheter could not be turned from the iliac artery to the aorta. A guide wire was passed through a tortuous arterial segment, and the balloon was then advanced.

Complications: Only transient signs of limb ischemia or arterial occlusion were noted in any patient in this series. No permanent complications occurred, and no patient required removal of the balloon catheter because of limb ischemia. No embolic phenomena were detected.

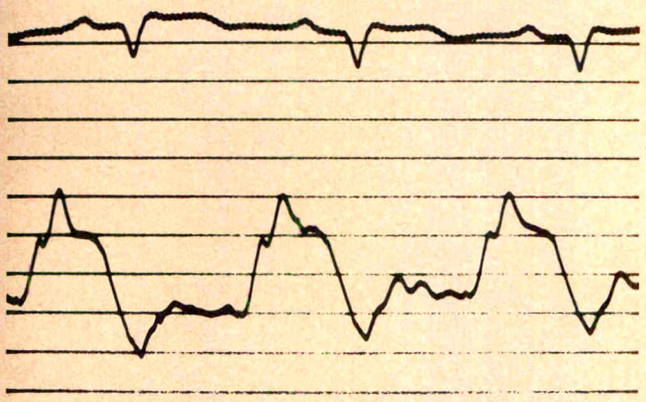


FIGURE 4. Arterial pressure tracing **(bottom)** recorded from the modified intraaortic balloon catheter lumen. Note the diastolic augmentation and systolic unloading. The electrocardiogram is at **top.** The calibration lines each represent 20 mm Hg. Paper speed is 100 mm/sec.

Discussion

Complications of conventional intraaortic balloon insertion: Intraaortic balloon counterpulsation has become an accepted means of temporary support

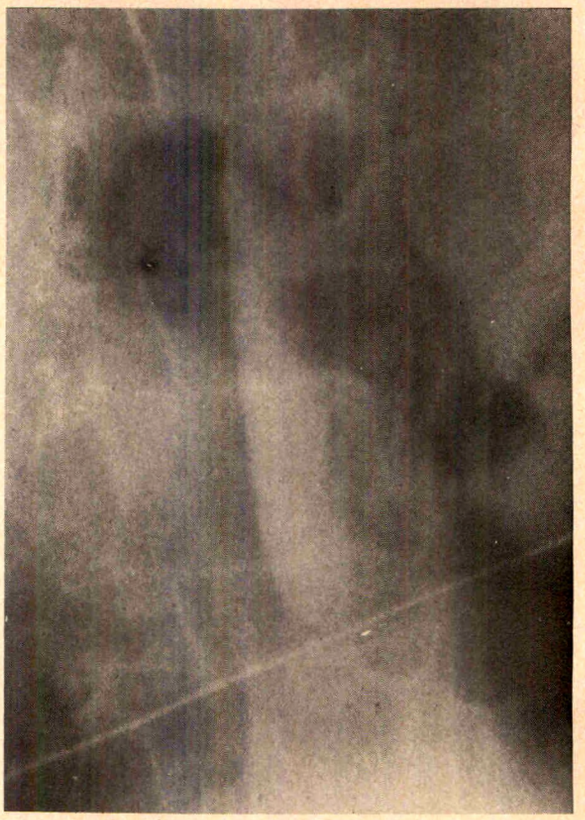


FIGURE 5. Arteriograms in a patient with intimal dissection. Contrast medium remains within the wall of the descending aorta 5 minutes after injection through a modified catheter. The procedure documented a dissection caused by a standard balloon catheter.

TABLE I

Summary of 16 Cases and Results of Balloon Insertion

Case no.	Age (yr) & Sex	Indication for IAB Placement	Unsuccessful Prior IAB Attempt	Evidence of Peripheral Vascular Disease	Time for Catheter Manipulation (min)	Guide Wire Required	Complications
1	36M	ICS	No	No	3	No	None
2	64M	ICS	Yes	Yes	30	Yes	Wire could not be advanced beyond plaque in iliac vessel. IAB not placed
3	69M	ICS	No	No	10	Yes	None
4	66F	ICS	Yes	Yes	10	Yes	None
5	65F	CS, VSD	Yes	Yes	30	Yes	None
6	66M	CS	No	Yes	8	Yes	None
7	61F	ICS	No	No	3	No	None
8	46M	ICS	No	Yes	10	Yes	DP pulse after IAB insertion. No limb ischemia
9	57M	ICS	No	No	10	Yes	None
10	50F	ICS	No	Yes	20	Yes	Transient limb ischemia resolving completely after 2 hours; ? spasm
11	55M	ICS	Yes	Yes	2	No	None
12	51F	MR	Yes	Yes	5	Yes	None
13	50M	ICS	No	No	5	No	None
14	57M	CS, AMR	No	Yes	6	Yes	None
15	67F	ICS	No	Yes	12	Yes	None
16	71M	ICS	No	Yes	5	Yes	None

AMR = acute mitral regurgitation; CS = cardiogenic shock; DP = decreased dorsalis pedis; IAB = intraaortic balloon; ICS = intermediate coronary syndrome; MR = mitral regurgitation; VSD = ventricular septal defect.

of severely compromised cardiac function or myocardial perfusion. However, definite limitations are placed on its effectiveness by the vascular tree into which the device must be placed. In a review of the vascular complications of balloon pumping, Alpert et al.[10] found arterial complications in 36 percent of treated patients who survived to have the balloons removed. Three of these complications were due to local trauma at the site of insertion and the remainder to arterial thrombi or occlusion of the femoral vessel by the catheter. This is similar to the incidence of ischemic complications in the cooperative clinical trial reported by Scheidt et al.[4] in which limb ischemia was experienced by 13 of 87 patients, 35 of whom survived to the have the balloon removed.

Aortic dissection, although less common, has also been reported with some frequency.[4,10–15] In a majority of cases the dissection was not suspected clinically but discovered at autopsy. In several cases the authors[10,11,15] observed that adequate diastolic augmentation was achieved although the balloon was extraluminal.

Although not considered a complication as such, clinically indicated intraaortic balloon counterpulsation cannot be instituted in some patients because the catheter cannot be placed. In the series of Alpert et al.,[10] this problem occurred in 5 of 84 attempts (6 percent). A similar incidence rate was reported by Kantrowitz et al.[12] (10 percent) and O'Rourke et al.[14] (5 percent) and a somewhat higher rate by Bregman et al.[17] (29 percent).

We have reviewed our experience at this center with 287 attempted insertions of the conventional AVCO intraaortic balloon. Peripheral vascular disease prevented placement of the balloon in 17 patients (6 percent), intimal aortic dissection was proved with angiography or at autopsy in six cases (2 percent) (Fig. 5 and 6) and, in an additional five patients, dissection was strongly suspected from clinical criteria, yielding an overall incidence rate of 4 percent. As noted previously, adequate diastolic augmentation was achieved in the majority of patients in whom dissection was later proved, and it was only at some time after balloon placement that widening of the mediastinum, pain or a decrease in hematocrit raised the suspicion that dissection might have occurred. In two patients the dissection was clinically silent and was documented only at autopsy. Dissection did not lead to death in any of our 11 patients in whom it was documented or strongly suspected, although others[18] have recognized it as a fatal complication of balloon insertion.

The standard technique for balloon insertion is a blind process, which is the principal factor contributing

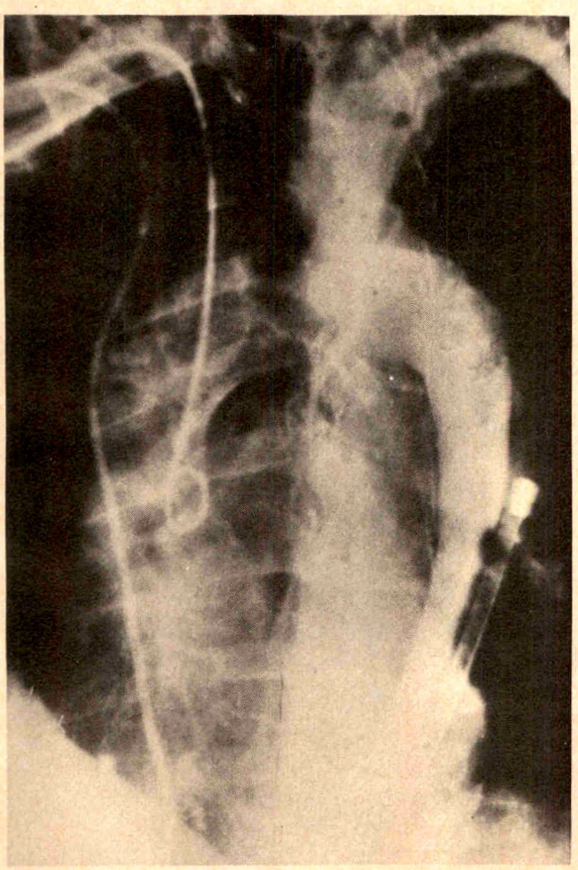


FIGURE 6. Aortogram in a patient with intimal dissection. The extravascular location of an intraaortic balloon catheter introduced by the standard "blind" technique is evident. Only minimal resistance to passage had been noted. Good diastolic augmentation was achieved with the balloon in this position.

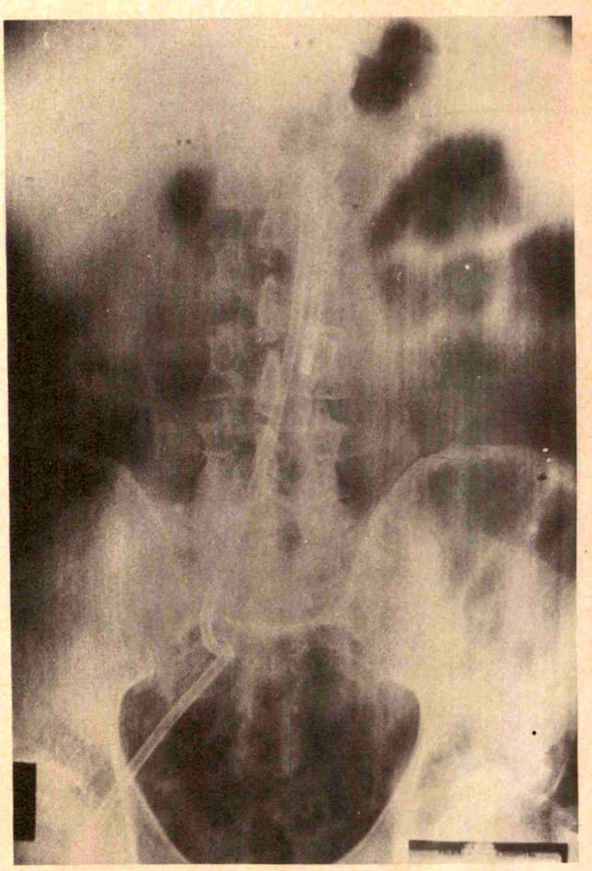


FIGURE 7. X-ray frame showing a standard intraaortic balloon that is kinked at the femoral insertion site and totally redundant upon itself in the abdominal aorta.

to these vascular complications. Other than fluoroscopy, there is no effective means of monitoring the progress of the standard balloon catheter. Figure 7 documents marked kinking of intraaortic balloon catheter that was not suspected until a postinsertion X-ray film was obtained.

Advantages of modified intraaortic balloon catheter: This study presents clinical experience with a balloon modification designed to introduce standard cardiac catheterization techniques into this field. The addition of a central lumen to the standard intraaortic balloon catheter has three distinct benefits: (1) It enables placement of the catheter with continuous monitoring of the arterial pulse wave. Damping of the pressure tracing provides an early clue to the presence of obstruction and, importantly, to the possibility of intimal dissection. Once the balloon is in position, the pressure tracing can be used to time inflation and deflation in order to provide maximal diastolic augmentation. Subsequently, the patient's arterial pressure can be constantly monitored without having to place a second arterial line. (2) The central lumen can be used to inject contrast medium to outline the arterial anatomy and identify the nature of obstructions encountered. Intimal dissection can be definitively documented by the failure of injected contrast material to wash away. Proper placement of the catheter distal to the left subclavian artery can also be confirmed with use of contrast agent. (3) A guide wire can be passed through the catheter to aid in negotiating difficult vascular anatomy and to maintain the balloon in the lumen in a difficult passage.

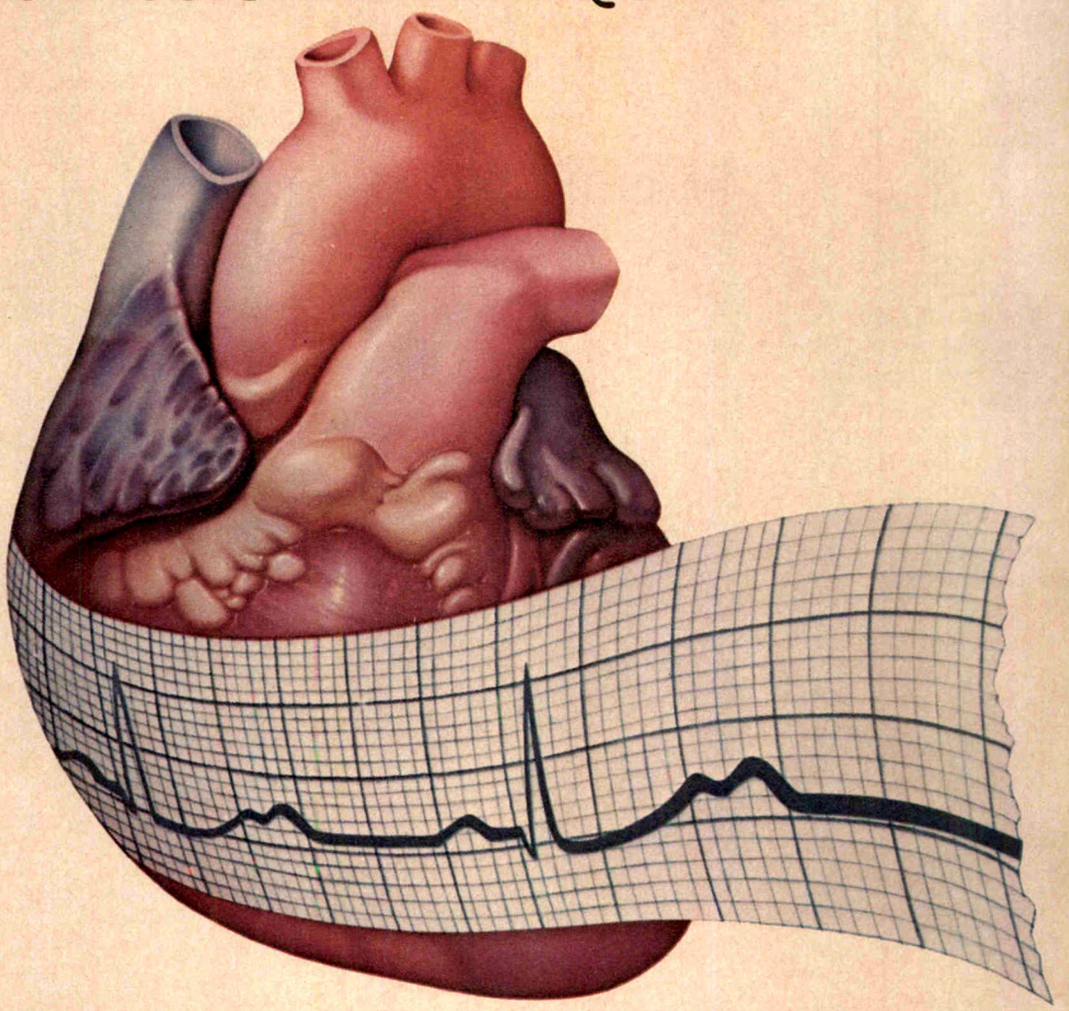
Clinical experience: Our experience with use of the modified balloon catheter suggests that it increases both the safety and efficacy of balloon insertion. It succeeded in four of five patients in whom insertion of a standard catheter was attempted and failed. In a further six patients with severe peripheral vascular disease, injection of contrast medium and use of a guide wire enabled successful insertion of the modified catheter after an initial attempt at passage with pressure monitoring alone had failed. It is possible that repeated attempts to insert a standard balloon catheter might have succeeded in this group, but such attempts would have been attended by an increased risk of intimal dissection or thromboembolism. These complications were avoided with use of contrast injection and a guide wire. There appears to be no significant risk produced by the addition of the central lumen itself. The lumen and connector were examined after balloon removal in all cases and no gross thrombus was found. No detectable thromboembolic complications occurred in the patients after balloon insertion. Although one patient experienced transient symptoms and another had diminution of distal pulses, neither required cessation of counterpulsation or had evidence of thrombus at the time of balloon removal. Spasm of the artery or obstruction of blood flow by the catheter itself probably accounted for these transient findings.

The addition of a central lumen to the intraaortic balloon catheter appears to be a modification that will significantly reduce the incidence of balloon-related vascular complications and failures of insertion experienced with the standard balloon catheter.

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Contraindications: In patients with hyperkalemia, chronic renal failure, systemic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

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Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

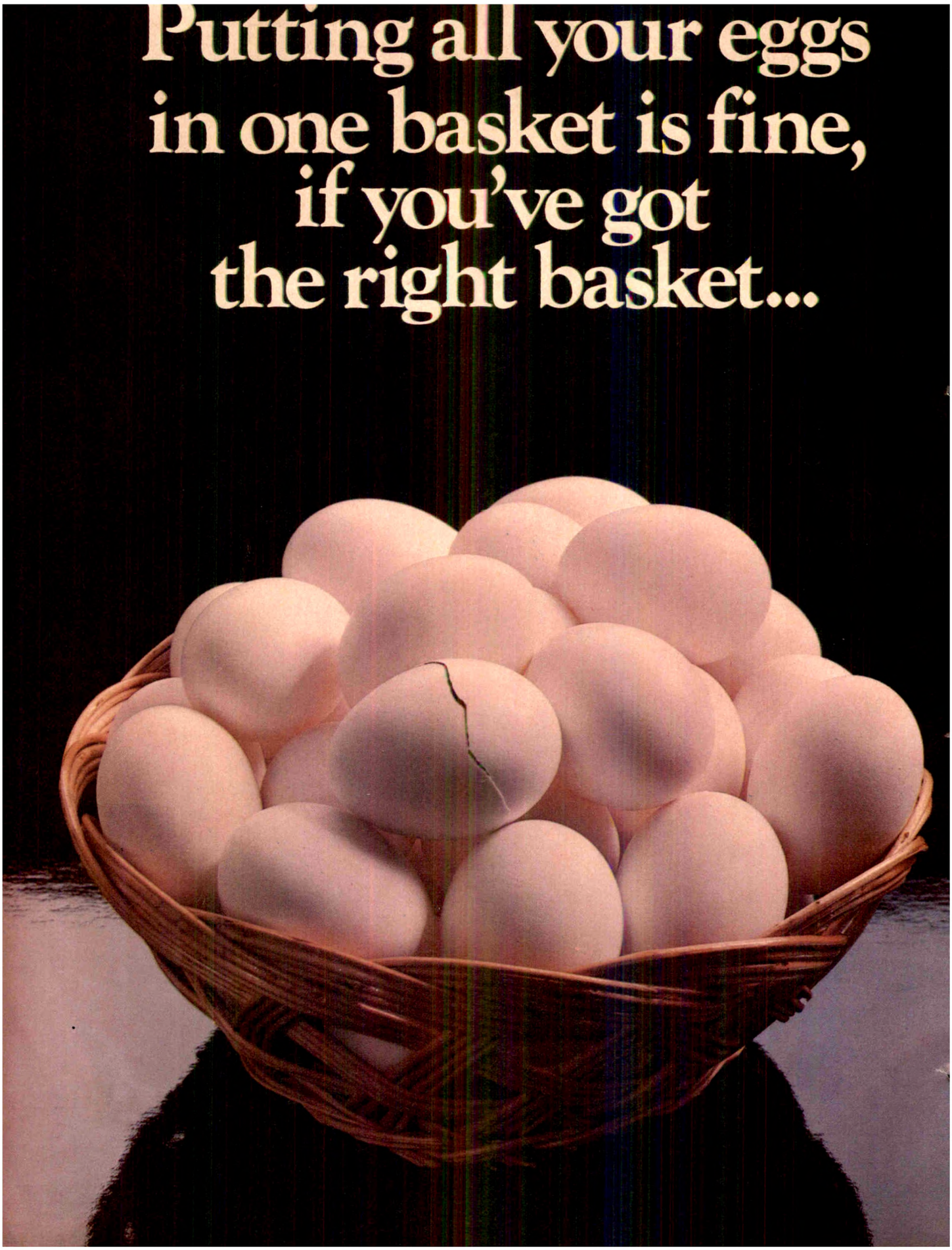
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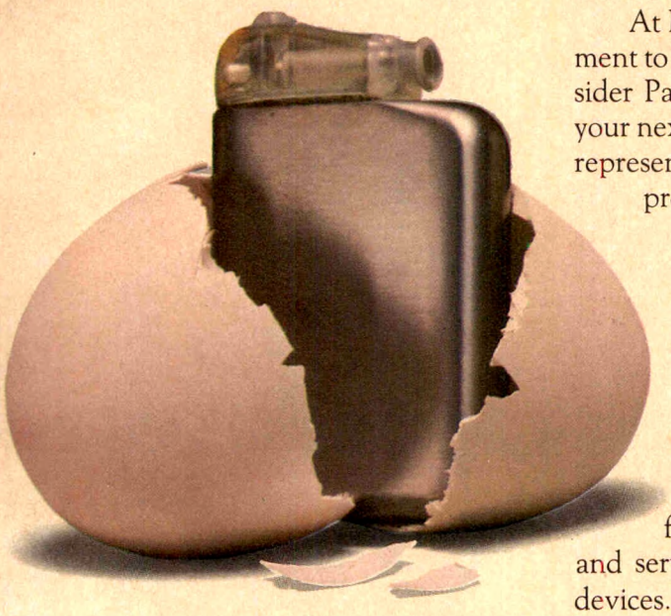
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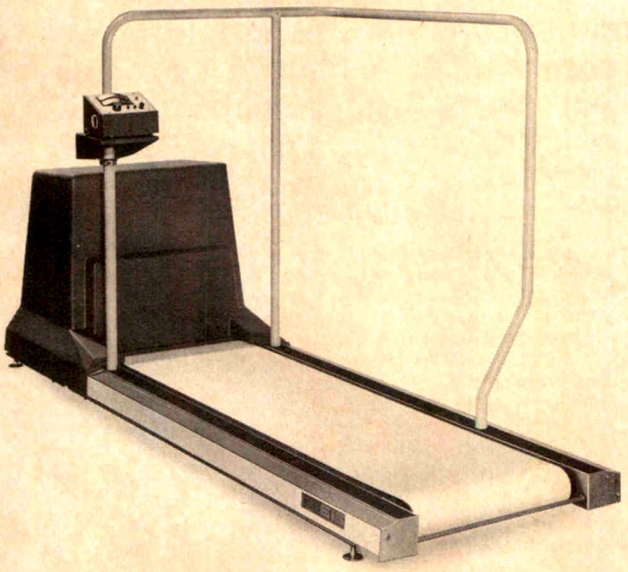
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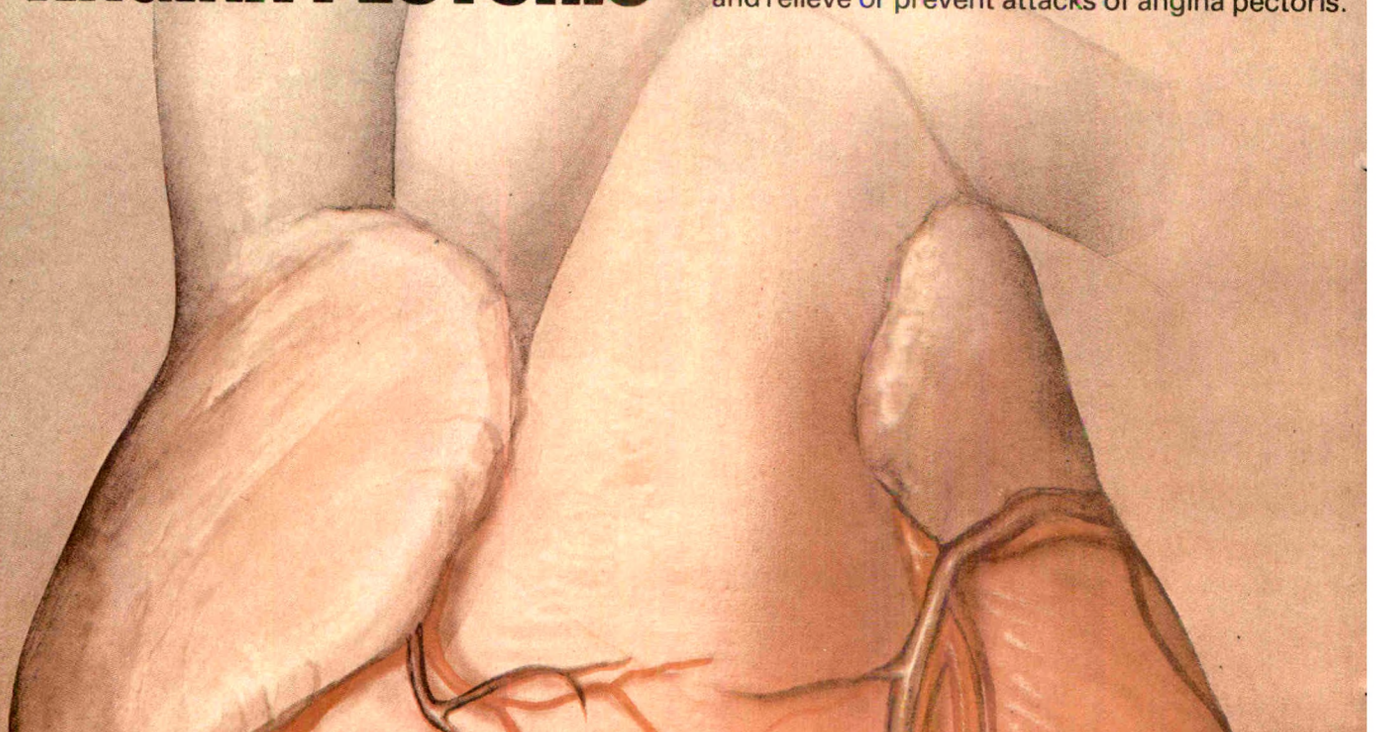


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Final classification of the less-than-effective indications requires further investigation.

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Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

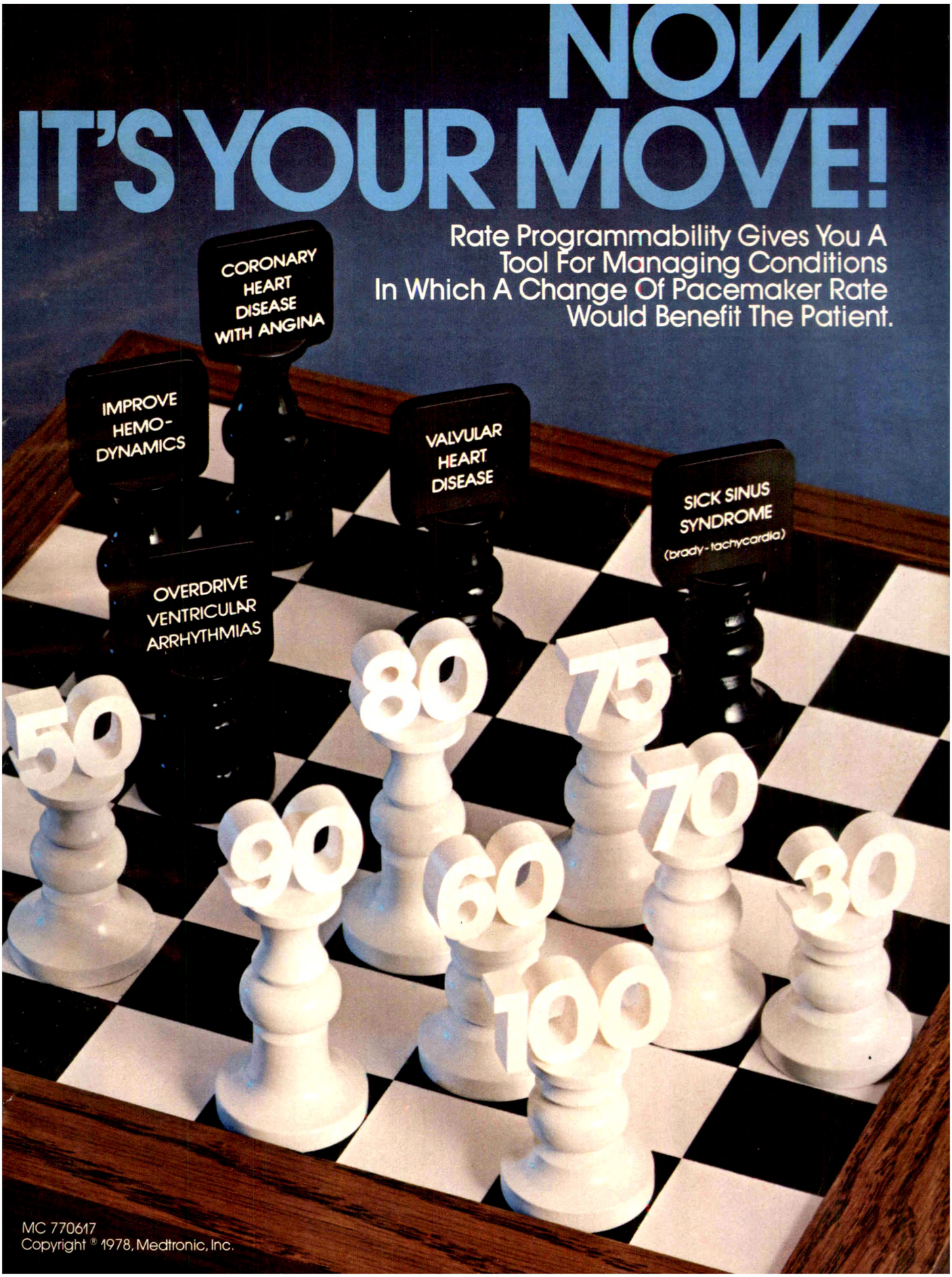
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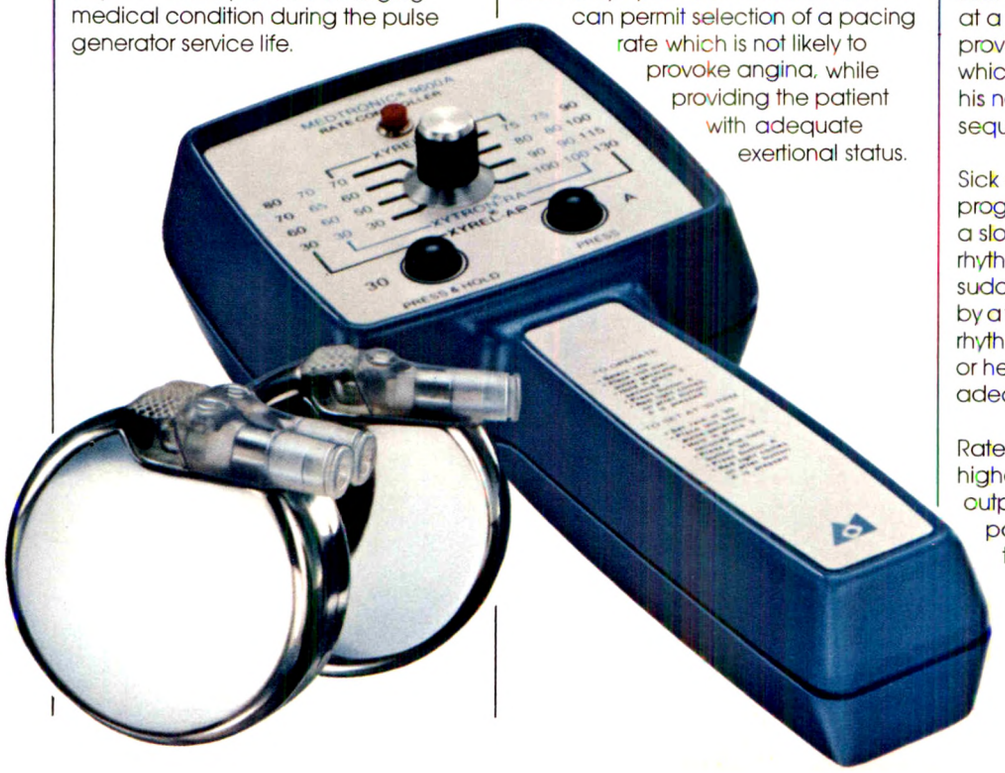

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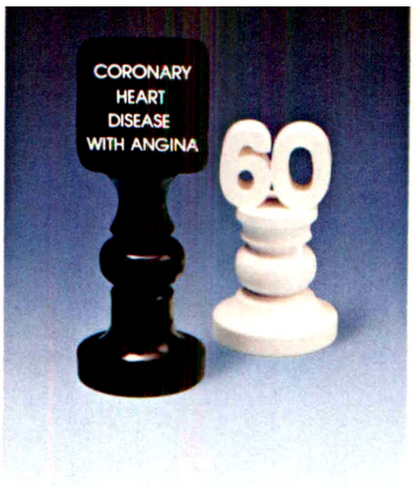
THERE ARE AT LEAST FIVE APPLICATIONS IN WHICH HAVING THE FLEXIBILITY OF CHANGING PACED RATE CAN PROVIDE MORE VERSATILITY IN PATIENT MANAGEMENT.

These applications are:

1. Sick Sinus Syndrome (brady-tachycardia).
2. Coronary heart disease with angina pectoris.
3. Valvular heart disease.
4. To overdrive ventricular arrhythmias.
5. To improve hemodynamics.

In each of these, having the ability to change the pacing rate can preserve, maintain or improve the quality of life for pacemaker patients. Furthermore, because of the potential longevity of lithium pacemakers, the physician can take advantage of the greater flexibility provided by rate programmability to respond to the patient's changing medical condition during the pulse generator service life.





USING RATE PROGRAMMABLE PACEMAKERS IN CORONARY HEART DISEASE WITH ANGINA PECTORIS

Not infrequently, the patient in whom pacing is indicated presents with coronary artery disease and angina pectoris.

Angina may be occurring as a consequence of heart rate exceeding the ability of the coronary artery network to provide adequate circulation to myocardial tissue. Since heart tissues receive nutrients during diastole, it is felt that a slower heart rate and a corresponding longer diastolic period may provide enhanced opportunity for energy and oxygen transfer to myocardial tissue.

In any event, a rate programmable pacemaker permits evaluation for clinical symptoms at various rates and can permit selection of a pacing rate which is not likely to provoke angina, while providing the patient with adequate exertional status.



THE APPLICATION OF RATE PROGRAMMING IN BRADY-TACHYCARDIA (SICK SINUS SYNDROME).

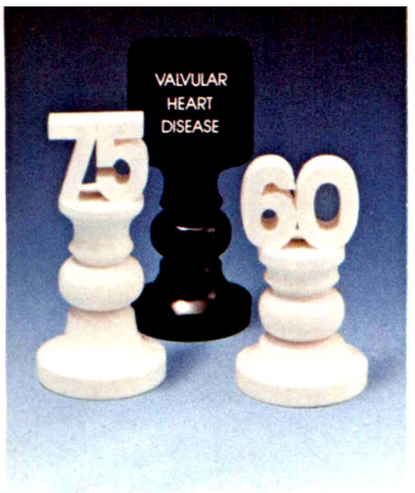
After the physician has determined that artificial heart pacemaking is the treatment of choice for the patient with brady-tachycardia, he may contemplate application of a rate-programmable pacemaker to treat this disease.

Because brady-tachycardia may be a progressive disease, it is often appropriate to implant a rate-programmable pacemaker.

For example, in the early stages of the disorder, the patient may require pacing for just a few seconds a month when the intrinsic rate drops below a rate which the physician has determined provides adequate cardiac output. In such a situation, the pacemaker is set at a low rate (i.e., 50 or 60 ppm) to provide an underlying safe rhythm, but which allows the patient the benefit of his normal atrial ventricular contraction sequence.

Sick sinus syndrome at times is a progressive disorder which may result in a slowing of the patient's normal sinus rhythm. This slowing may be gradual or sudden. Frequently, it is accompanied by a tendency towards a more unreliable rhythm. The patient, thus, increases his or her reliance on the pacemaker for adequate heart rate.

Rate programming at increasingly higher rates may help maintain cardiac output at adequate levels when the pacemaker is needed to provide the dominant rhythm. An increase in pacemaker rate may also be needed to prevent the emergence of a less suitable tachyarrhythmia.



THE APPLICATION OF RATE PROGRAMMABLE PULSE GENERATORS IN VALVULAR HEART DISEASE

The clinical course for pacemaker patients with valvular heart disease is complex and unpredictable.

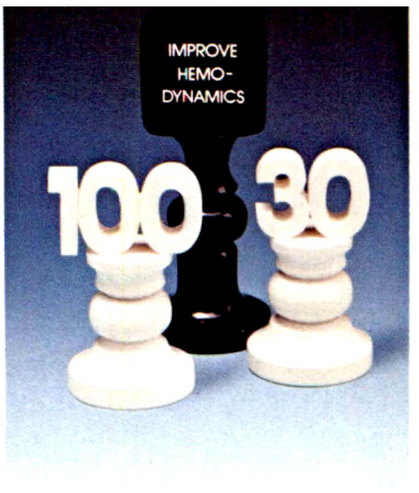
Many of these patients require a pacemaker prior to operation for their valve lesion.

The patient with aortic stenosis may need to have his rate adjusted to a slow level to allow for complete emptying of the ventricle. Too fast a rate increases ventricular pressure and restricts the flow of blood from the coronary arteries to the endocardium, resulting in subendocardial ischemia. There is some evidence that pacing at typical fixed pacemaker rates may actually cause patients with aortic stenosis to lose cardiac output and have decreased perfusion pressure.

On the other hand, the patient with aortic insufficiency has regurgitation backwards into the ventricle. A slow rate allows more blood to flow backwards, increasing volume and ventricular pressure. This also restricts blood flow from the coronary arteries to the endocardium, again resulting in subendocardial ischemia. A faster paced rate may help control the condition. Of course, the best rate for perfusing the endocardium for either condition varies considerably between patients.

Rate requirements will probably change a great deal when a prosthetic valve replacement is made.

Typically, any patient with valvular heart disease who requires a pacemaker could benefit from the flexibility a rate-programmable pacemaker offers in this complex, unpredictable disorder.



CHANGING RATE TO ENHANCE THE METABOLIC STATE THROUGH IMPROVED HEMODYNAMICS

Conditions of disease, or certain medical treatments, can affect a patient's metabolic requirements. Pacemaker patients are, because of their age and underlying heart disease, prone to various medical problems, including myocardial infarction, angina and congestive heart failure.

By having the ability to alter the diseased or ill patient's heart rate, the physician can optimize the rate for maximum cardiac output and organ perfusion without affecting (or with minor effects) on myocardial oxygen uptake. Also, in some MI patients a rate can be found which produces increased cardiac output with decreased left ventricular filling pressure. Rate changes may also affect and improve a patient's mental state and enhance the ability to perform even mild exercise. When a pacemaker is implanted, the patient is ill (i.e. bed-ridden). An adequate rate under those conditions may not be adequate when the patient is up and about.



USE OF RATE PROGRAMMABLE PACEMAKERS TO CONTROL VENTRICULAR ARRHYTHMIAS

Ectopic ventricular activity can be suppressed by permanent pacing. However, the slowest paced rate at which ventricular arrhythmias will be controlled is unpredictable, and changeable. It is not unusual for the rate at which PVC's occur to change as the patient's underlying heart disease progresses.

Pacing in the presence of PVC's often involves considerable adjusting of rate as the physician determines the paced rate which will be just slightly higher than the rate at which the ectopic foci discharge. This rate may involve a compromise, for an optimal rate for achieving maximal cardiac output may not coincide with the best rate for suppressing ectopic activity. Indeed some pacemaker rates tend to excite reentry pathways causing the extra-systole.

For these reasons, having the opportunity to change rate can assist the physician in arrhythmia control.

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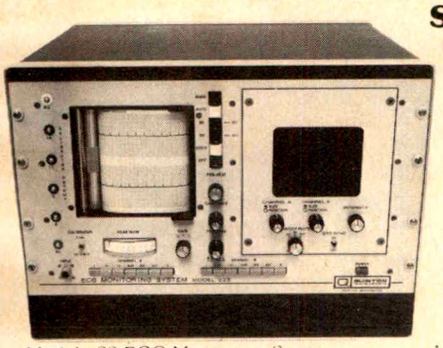


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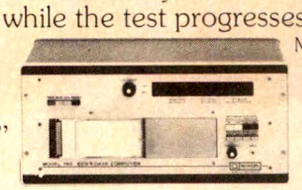
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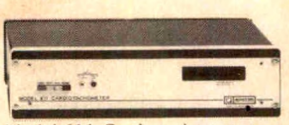


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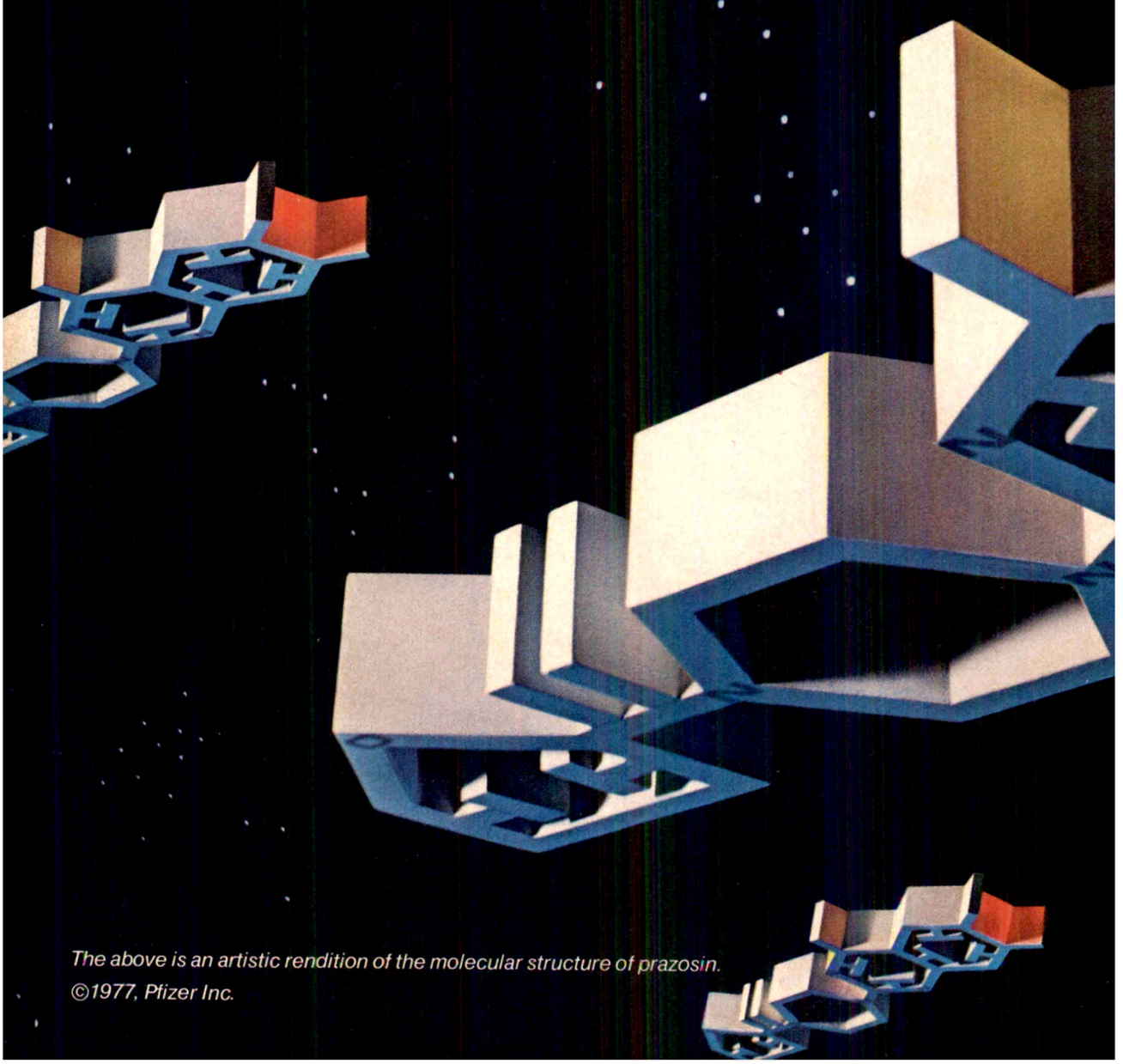
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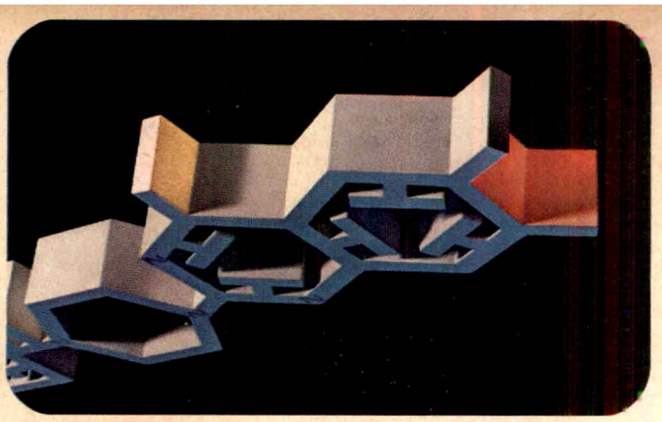
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- Starting dosage: 1 mg t.i.d.
- Usual maximum recommended dosage: 20 mg daily, given in divided doses.
- Some patients can be maintained adequately on a b.i.d. dosage regimen.
- Available in 1-mg, 2-mg, and 5-mg capsules.

BRIEF SUMMARY

MINIPRESS® (prazosin hydrochloride) Capsules *For Oral Use*

INDICATIONS. MINIPRESS (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS. MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS. The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION. The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. Higher doses usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED. MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437), and 5 mg (blue and white #438) capsules in bottles of 250, and unit dose packages of 100 (10 x 10's).

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*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

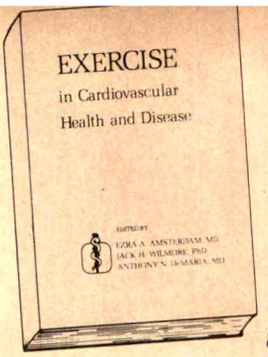
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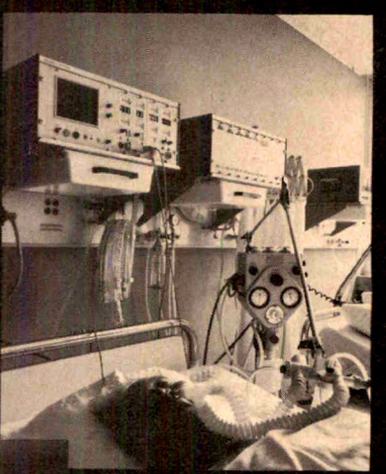
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Pathologic Anatomy of Ebstein's Anomaly of the Heart Revisited

KENNETH R. ANDERSON, MBChB, FRCPA
J. T. LIE, MD, FACC

Rochester, Minnesota

The typical textbook description of Ebstein's anomaly of the heart usually singles out and emphasizes the downward displacement of septal and posterior leaflets of the tricuspid valve. An anatomic reappraisal of this uncommon anomaly suggests that other structural abnormalities of import should be equally stressed. Among the 15 well preserved autopsy specimens in this series, enlargement of the right atrioventricular (A-V) junction and malalignment of the giant and sometimes muscularized anterior leaflet of the tricuspid valve were consistently found. In addition, massive aneurysmal dilation of the right ventricle was present in almost two thirds (9 of 15) of the hearts. Our observations raise the possibility that abnormal embryonic development of the right A-V junction may be the primary event that leads to malformation of the tricuspid valve apparatus.

Ebstein's anomaly of the tricuspid valve is an uncommon developmental abnormality that accounts for less than 1 percent of all congenital cardiac malformations.[1] This curious anomaly has a varied pathologic anatomy and, according to a large scale international cooperative study,[2] a varied natural history. The variable clinical course is not well explained by the spectrum of structural abnormalities. Several surgical procedures have been developed to correct Ebstein's anomaly, but in general the results have been relatively disappointing.[3–6]

The purpose of this reappraisal of Ebstein's anomaly is to draw attention to certain anatomic features of the anomaly that have received less emphasis in the past and that may have relevance in the clinical assessment and surgical correction of this anomaly. A more complete understanding of the anatomic derangements may also shed new light on the possible embryogenesis of Ebstein's anomaly.

Materials and Methods

There were 20 autopsy specimens of classic Ebstein's anomaly without transposition of the great arteries in the existing collection of hearts with congenital cardiac disease of the Mayo Clinic Department of Pathology and Anatomy. Five hearts were excluded because previous pathologic examination made them unsuitable for detailed anatomic study. The remaining 15 hearts formed the basis of this report.

Measurements of selected features were made in an attempt to define the anatomic pattern of structural abnormalities in hearts with Ebstein's anomaly. These measurements included the circumference of the right and left atrioventricular (A-V) junctions, the maximal displacement of the tricuspid valve leaflets, distance from the apex to the semilunar valve in the right and left ventricles and distance from the apex to the posterior A-V junction in the right ventricle.

Histologic evaluations were made of the selected hearts with special reference to (1) the musculature of the aneurysmally dilated right ventricular "wall," (2) the presence or absence of muscle fibers in the anterior leaflet of the tricuspid valve, and (3) the displaced septal and posterior leaflets to determine whether

From the Department of Pathology and Anatomy, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. Dr. Anderson is a New Zealand National Heart Foundation Fellow in Cardiovascular Pathology. Manuscript received June 27, 1977; revised manuscript received October 10, 1977, accepted October 12, 1977.

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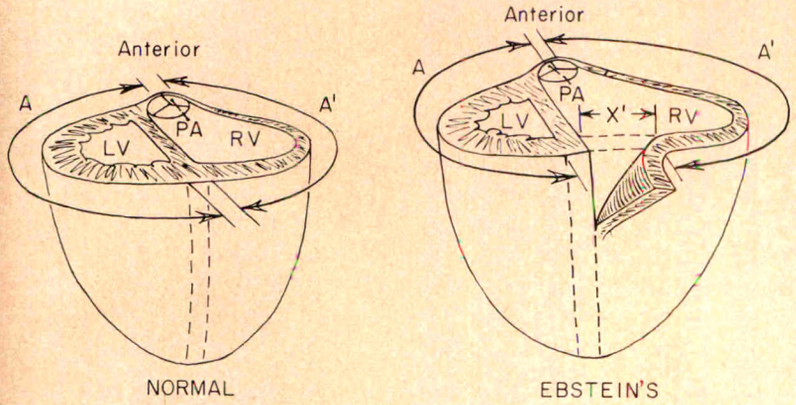


FIGURE 1. The ventricles viewed from the back. **Left,** in the heart, the distance around the left border of the heart from the pulmonary valve to the posterior interventricular septum, at the level of the atrioventricular groove (A) is approximately the same as the distance similarly measured around the right border (A′). **Right,** in the heart with Ebstein's anomaly, similar measurements reveal that the distance around the right border is considerably longer than the distance around the left border. The added distance (X′) corresponds approximately to the aneurysmally dilated portion of the right ventricular wall. LV = left ventricle; PA = pulmonary artery; RV = right ventricle.

the leaflet tissue was in continuity with the thickened endocardium of the wall of the inflow (atrial) chamber.

The coronary arterial anatomy was examined in each heart and particular note was made of the coronary arteries in the right A-V groove where they might be in danger of being injured by plication procedures for the surgical correction of the incompetent malformed tricuspid valve.

Results

The A-V junction: In all 15 hearts studied, the ring where the right atrium joined the right ventricle (right A-V junction) did not correspond to the ring of attachment of the A-V valve leaflets (tricuspid valve ring). A consistent finding in Ebstein's anomaly was enlargement of the right compared with the left A-V junction. This enlargement was readily apparent after comparing the distances around the A-V junction on either side from the pulmonary valve to the posterior interventricular septum (Fig. 1). In six normal hearts from patients of various ages these measurements were approximately equal, with the left A-V junction usually measuring slightly more than the right A-V junction. In the hearts with Ebstein's anomaly, the measurement of the right A-V junction was 1.2 to 2.2 times greater than the left measurement (Table I). Comparison with other measurements, such as the apex to aortic valve distance of the left ventricle, demonstrated that the inequality of the A-V junction circumferences was due to an absolute increase in size of the right A-V junction rather than a decreased size of the left junction. Among hearts with a posterior aneurysm, the increased circumference of the right A-V junction approximately corresponded to the circumference of the aneurysm (X′ in Fig. 1).

The tricuspid valve: When viewed from the right atrium, the typical deformity of the tricuspid valve in all hearts with Ebstein's anomaly was clearly apparent.

TABLE I

Ebstein's Anomaly: Atrioventricular Junction Measurements and Associated Anomalies

Case no.	Age	Sex	A-V Junction (mm) Right	A-V Junction (mm) Left	A-V Junction Ratio (R/L)	Associated Anomalies
			Right Ventricle Massively Dilated			
1	1 day	M	60	45	1.3	ASD
2	5 days	F	60	40	1.5	PFO
3	18 mo	M	110	65	1.7	ASD, PS
4	2 yr	F	100	60	1.7	ASD
5	6 yr	M	110	60	1.8	ASD
6	13 yr	F	150*	80*	1.9*	PFO
7	14 yr	M	110	70	1.6	. . .
8	15 yr	M	180	90	2.0	ASD, LSVC
9	18 yr	M	160	80	2.0	PFO
			Right Ventricle Moderately Dilated			
10	12 yr	M	110	60	1.8	PFO
			Right Ventricle Not Dilated			
11	7 days	F	55	40	1.4	PFO
12	9 days	F	60	35	1.7	PFO
13	2 yr	F	110	50	2.2	ASD, PAtr
14	3 yr	M	100	85	1.2	PFO, VSD
15	51 yr	F	180	100	1.8	PFO

* Estimated.

A-V = atrioventricular; LSVC = persistent left superior vena cava; PAtr = pulmonary atresia; PFO = patent foramen ovale; PS = pulmonary stenosis; R/L = right to left; VSD = ventricular septal defect.

The anterior leaflet was attached to the A-V junction in the correct position with the medial margin of the attachment contiguous with the anterior border of the septal leaflet at the membranous septum. As the observer's eye moved posteriorly, the attachment of the septal leaflet was seen to be progressively displaced downward. Rather than being attached normally just below the A-V junction, it was attached to the ventricular septum, leaving a triangular portion of the ventricular septum exposed to the atrium (Fig. 2). At the posterior border of the ventricular septum, the septal leaflet met the posterior leaflet, whose attachment at this point was also displaced well below the A-V junction. As the observer's eye then moved laterally, along the posterior wall of the ventricle, the attachment of the posterior leaflet angled upward so that, at the lateral aspect of the valve, it met the attachment of the anterior leaflet to the A-V junction. The point of maximal displacement of the tricuspid valve leaflets was where the septal leaflet met the posterior leaflet on the posteromedial aspect of the right ventricular wall.

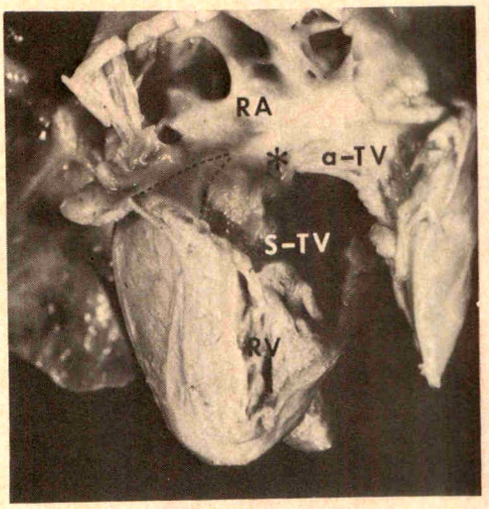


FIGURE 2. A view of the right atrium (RA), right ventricle (RV) and tricuspid valve looking toward the ventricular septum. The insertion of the septal leaflet (S-TV) meets the insertion of the anterior leaflet (a-TV) on the membranous septum **(asterisk)**. Progressing posteriorly, the insertion of the septal leaflet is displaced into the ventricle, thus exposing a triangular area of ventricular septal wall to the right atrium (**broken lines** enclose ventricular septum exposed to the atrium).

The anterior leaflet: Although the anular attachments were similar, the size, shape and construction of the anterior leaflet in Ebstein's anomaly bore little resemblance to its counterpart in the normal heart (Fig. 3). It was considerably larger and structurally quite different. From the right margin of its insertion into the A-V junction, the lateral edge of anterior leaflet passed downward and medially, approximately parallel and close to the acute border of the heart. In contrast to the normal tricuspid valve, in which this edge is entirely free, in Ebstein's anomaly it was attached variably to the ventricular wall. In 10 hearts, attachment was made by several abnormal papillary muscles and chordae tendineae, whereas in 5, there was continuous uninterrupted muscular attachment of this edge of the leaflet to the ventricular wall. The markedly abnormal anterolateral papillary muscle was situated at the lower extent of the lateral edge. This muscle varied from a broad-based linear sheet to a more discrete muscle belly, but it was often difficult to separate visually the papillary muscle proper from the attachment of the lateral edge of the leaflet to the ventricular wall. When this attachment was uninterrupted, it was often directly continuous with the papillary muscle.

From the anterolateral papillary muscle, the rather taut anterior free edge of the leaflet extended in a direct line to its chordal attachment to the crista supraventricularis (infundibular septum). This free edge was often slightly thickened. This chordal attachment was remarkably constant in that it always reached the apex of the inverted V formed by the junction of the septal and parietal limbs of the crista. In the heart with Ebstein's anomaly, as in the normal heart, a fibrous ridge sometimes described as a fusion line may be seen at the apex of the crista. In the normal heart, the muscle of Lancisi is attached to the septal limb of the crista some distance from the cristal apex. In hearts with Ebstein's

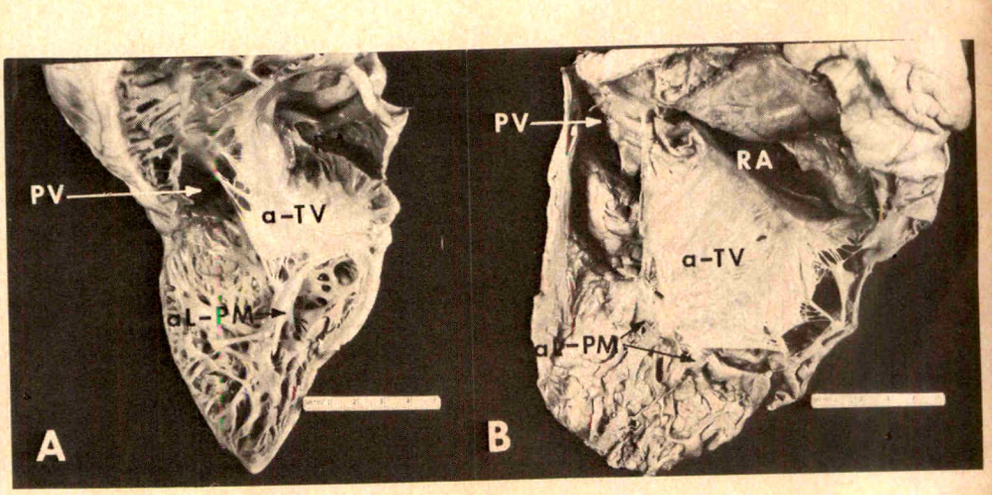


FIGURE 3. The parietal wall of the right ventricle with the anterior leaflet of the tricuspid valve (a-TV) attached, viewed as if looking toward the right side from within the cavity of the right ventricle. **A,** in a normal heart; **B,** in a heart with Ebstein's anomaly. The anterior leaflet in the latter heart is greatly enlarged and abnormal in configuration. The anterolateral papillary muscle (aL-PM) is poorly formed and the leaflet is tethered to the posterior right ventricular wall by abnormal chordal attachments. PV = pulmonary valve; RA = right atrium.

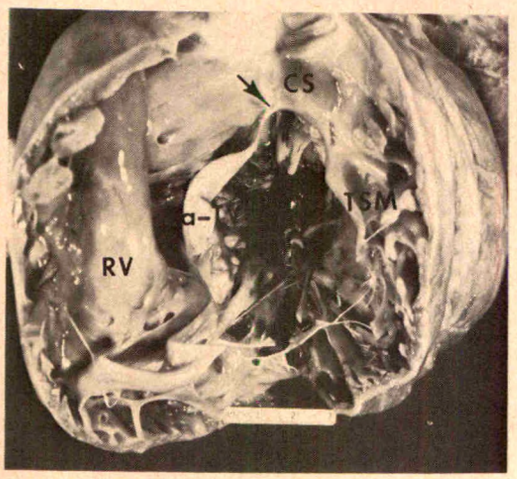


FIGURE 4, left. The right ventricle (RV) in Ebstein's anomaly. The anterior leaflet of the tricuspid valve (a-TV) is attached by chordae to the apex of the inverted V formed by the crista supraventricularis (CS) **(arrow)**. A fibrous raphe sometimes may be visible here in both normal and congenitally malformed hearts. In the normal heart, the anterior leaflet of the tricuspid valve is attached to the septal bar of the crista some distance from the cristal apex. This attachment may be chordal or there may be a small papillary muscle (muscle of Lancisi). In Ebstein's anomaly, the attachment is always chordal in nature. TSM = trabeculae septomarginalis.

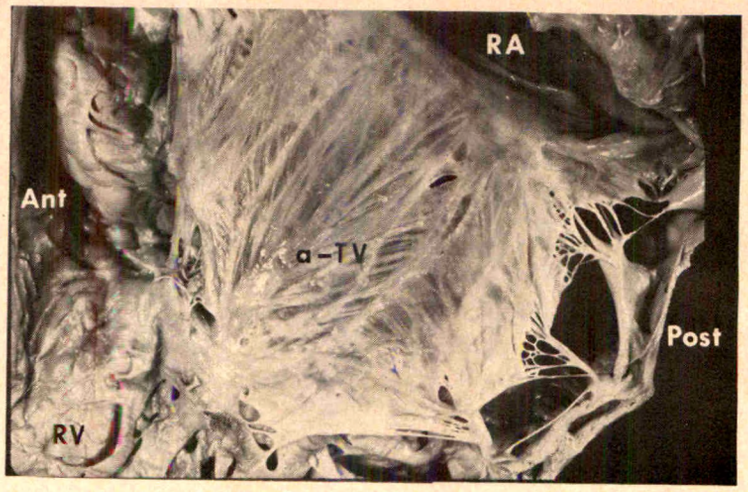


FIGURE 5, right. Close-up view of the anterior leaflet of the tricuspid valve (a-TV) in Ebstein's anomaly showing the abnormal structure of the leaflet with fibrous strands incorporated in the leaflet stretching between its attachments to the right A-V junction and the right ventricular (RV) wall. These strands are in part muscular and in part fibrous. Ant = anterior; Post = posterior; RA = right atrium.

anomaly, the chordal attachment of the anterior leaflet was always directly into the mid line of the crista (Fig. 4).

The structure of the anterior leaflet was also distinctly abnormal. Instead of being entirely a fibrous membrane, as in the normal heart, this leaflet was composed of easily visualized strands, stretching from the anterolateral papillary muscle to the insertion of the leaflet into the A-V junction (Fig. 5). These strands fanned out radially from the anterolateral muscle toward the attachment of the leaflet at the A-V junction. In one heart these strands were entirely composed of muscle, but in other hearts they were partly muscular and partly fibrous. Thus, muscular continuity appeared to exist from the anterolateral papillary muscle and the parietal right ventricular wall to the tricuspid valve ring at the right A-V junction.

The septal and posterior (inferior) leaflets: The attachment of these leaflets in hearts with Ebstein's anomaly was displaced below the A-V junction, thus exposing a triangular area of ventricular wall to the right atrium. The degree of displacement varied and determined the relative size of the partitioned parts of the right ventricle. Greater displacement toward the apex resulted in a smaller functional right ventricle (distal chamber) and a larger "atrialized ventricle" (proximal chamber). The attachment of the septal leaflet was often displaced down to the trabecula septomarginalis (moderator band). The mobile part of the leaflet, always abnormal, varied markedly in size. There were often recesses in the right ventricle created by excessive tenting of the mobile part of the septal leaflet. In all hearts studied, both the septal and the posterior leaflets had abnormal chordal attachments. Like the septal leaflet, the posterior leaflet was thickened, and abnormal chordal attachments tethered it to the ventricular wall.

The right ventricle: The right ventricle was divided into two parts by the abnormal tricuspid valve. These are usually referred to as the proximal and distal chambers.

The proximal chamber was continuous with the right atrium through the now unguarded A-V junction and was thus a functional part of the right atrium. It has sometimes been referred to as the atrialized portion of

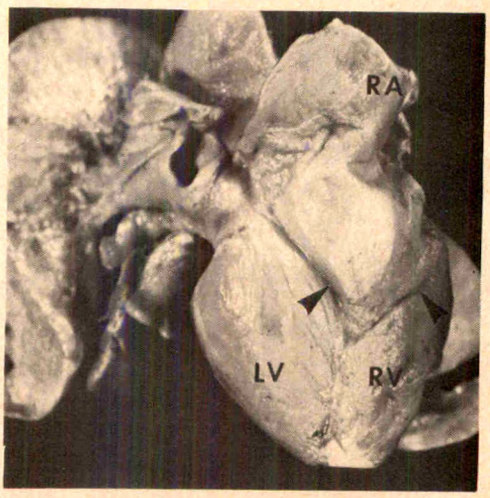


FIGURE 6. The external appearance of the posterior surface of a heart with Ebstein's anomaly and a normal-sized (undilated) right ventricle (RV). A triangular-shaped thin-walled area of aneurysmal dilatation of the right ventricle is present **(arrows)**. LV = left ventricle; RA = right atrium.

the right ventricle. The endocardium of this chamber was usually thick, fibrous and smooth, although some poorly formed trabeculae were sometimes present. The posterior wall corresponded approximately to the aneurysmally dilated portion of the right ventricle observed most noticeably in those hearts that did not have generalized right ventricular dilatation (Fig. 6). The wall of the "aneurysm" was often very thin with sparse muscle fibers. In two hearts, it was devoid of any muscle and composed entirely of fibrous tissue.

The distal chamber was, or constituted the functional unit of, the right ventricle. It communicated with the proximal chamber by way of the variably sized and usually incompetent orifice of the tricuspid valve. The distal chamber was composed of three parts—the infundibulum, the apical part of the ventricle and the anterolateral recess, which was an appendage-like recess of the distal chamber situated behind the anterior leaflet of the tricuspid valve (Fig. 7). The trabecula septomarginalis often formed a distinctive landmark in the distal chamber (Fig. 7).

Dilatation of the ventricle: In 9 of the 15 hearts with Ebstein's anomaly of the right-sided tricuspid valve, the right ventricle was markedly dilated and thin-walled (Fig. 8). Dilatation involved the entire free wall of the right ventricle, but the posteromedial wall was thinner than the remainder. This area corresponded to the area that may be an aneurysmal pouch in the undilated examples. Of the remaining six hearts, one showed a moderate degree of dilatation, and five were either normal or thick-walled with a chamber of normal size. Generalized dilatation of the ventricle was subjectively assessed and did not appear to be related to the degree of enlargement of the right A-V ring circumference (Table I). No specific feature of the malformation of the tricuspid valve stood out as being associated with dilatation.

The coronary arteries: The positions of the coronary ostia and the course of the proximal segments of the major main coronary arteries were similar to those in the normal heart. Special attention was directed to the topography of the coronary arterial anatomy at the posterior (inferior) surface of the heart because of surgical procedures involving plication of a portion of the right ventricular wall along the A-V groove. In five hearts the posterior descending artery was a branch of the left circumflex coronary artery, and in another five it was a branch of the right coronary artery. In the latter group, it seems inevitable that surgical plication of the posterior wall of the right ventricle would compromise the arterial circulation to the posterior ventricular wall. In the remaining five hearts, both the left circumflex and the right coronary arteries contributed to the descending branches.

Associated cardiac anomalies: All but 1 of the 15 hearts had a shunt at the atrial level, either an atrial septal defect or a patent foramen ovale. The only other cardiac anomalies were one example each of pulmonary atresia, pulmonary stenosis, ventricular septal defect and persistent left superior vena cava (Table I).

Discussion

Anatomic Features

In Ebstein's anomaly of the tricuspid valve considerable variation exists in the pathologic anatomy of the malformation and in the clinical course of the patients

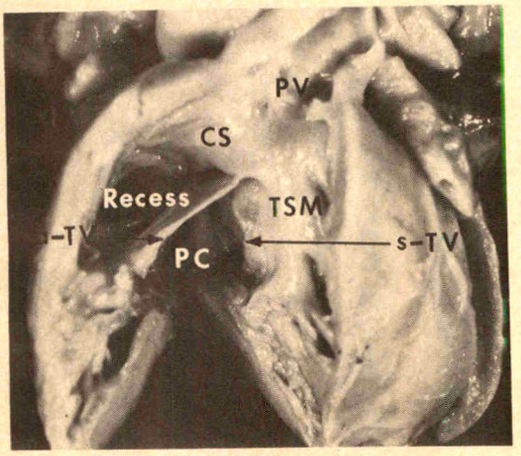


FIGURE 7. Anterior view of the opened right ventricle in Ebstein's anomaly. The anterior leaflet of the tricuspid valve (a-TV) separates the proximal chamber (PC) from the anterolateral recess of the distal chamber. The free edge of the anterior leaflet is attached below to the abnormally formed anterolateral papillary muscle and above to the apex formed by the junction of the two limbs of the crista supraventricularis (CS). The displaced septal leaflet (s-TV) is attached to a rather prominent trabecula septomarginalis (TSM). PV = pulmonary valve.

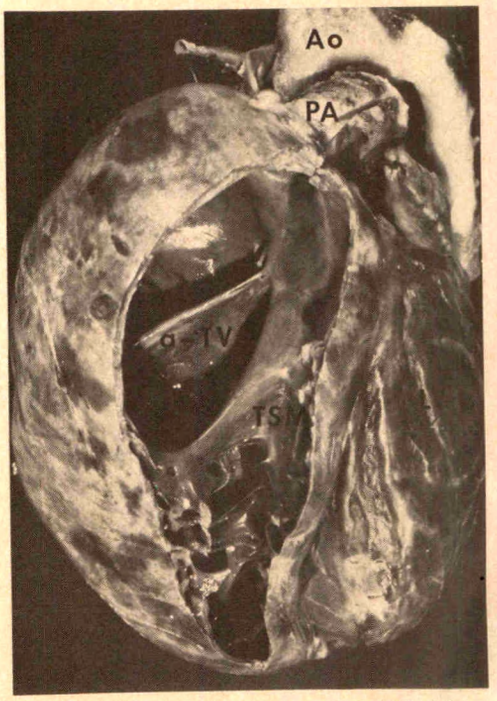


FIGURE 8. Massive dilatation of the right ventricle in Ebstein's anomaly. The right ventricle has been opened anteriorly. Ao = aorta; a-TV = anterior leaflet of the tricuspid valve; LV = left ventricle; PA = pulmonary artery; TSM = trabeculae septomarginalis.

so afflicted. Previously published anatomic studies have dealt with most features of the anatomy of the malformation in detail. These features include the displacement of the valve leaflets, the aneurysmally dilated posterior right ventricular wall[7] and its abnormal structure,[8] dysplastic changes in the valve leaflets,[9] the occasionally observed "plastered" down nature of the septal leaflet,[10,11] the architectural abnormality of the right ventricle[11] and the A-V specialized conducting tissue.[11–13] We observed these features in our study, but we emphasize certain points that have received less attention in the past.

Enlarged circumference of the right A-V junction: This was present in all our cases. It should not be confused with the tricuspid valve ring that in Ebstein's anomaly is displaced into the right ventricle. Yater and Shapiro[12] mentioned the enlargement of the right A-V orifice, and it was exemplified in their paper by a cited case report of Blackhall-Morison,[14] who noted that the "auriculoventricular orifice admitted the whole hand." The degree of enlargement of the right A-V junction circumference corresponded approximately to the width of the thinned segment of ventricular myocardium situated posteromedially (Fig. 1). This thinned segment of ventricular wall was frequently aneurysmally dilated, and in two hearts it was a well circumscribed fibrous sac completely devoid of myocardium.

Generalized dilatation of the entire right ventricle: This abnormality was also previously noted[7] and was a common feature in 64 percent (9 of 15) of the hearts in our study. It was evident in some of the neonatal examples but was more striking in the hearts from older patients. It was not observed in the oldest patient in our series (aged 51 years). Dilatation of this ventricle is probably in part an acquired phenomenon, but there is no sound hemodynamic explanation for massive dilatation. Dilatation of this degree has not been observed in other congenital valve disorders or in acquired disease of valve incompetence. Gross dilatation of a ventricle is usually associated with terminal cardiac failure or abnormalities of the ventricular myocardium such as congestive cardiomyopathy. We believe it is likely that some dilatation of the right ventricle is an integral component of Ebstein's anomaly, associated with (and possibly due to) deficiency of the myocardium of the right ventricle. It is our impression that massive dilatation of the right ventricle, when present, may be a limiting factor in achieving good results with surgical repair of Ebstein's anomaly.

Enlarged and abnormal anterior leaflet of tricuspid valve: The anterior leaflet in Ebstein's anomaly of the right-sided tricuspid valve is often markedly enlarged and abnormally structured. This leaflet has been described as a "trapeze-like" structure or a "sail" hanging down into the ventricle. The free edge is stretched between a malformed anterolateral papillary muscle and an abnormal chordal attachment to the very apex of the crista supraventricularis. This attachment is presumably the equivalent of the muscle of Lancisi that, in the normal heart, is an anchorage for the anterior leaflet of the tricuspid valve and is located at the septal band of the crista supraventricularis.

Embryologic Considerations

The valve leaflets: The A-V valves are formed relatively late in cardiac embryogenesis, some time after the A-V connections have been established. The importance of the contribution of ventricular wall myocardium to the actual structure of the primitive valve leaflets was well known to early workers, and this subject was reviewed by Odgers in 1937.[15] This has led to the commonly held belief that the leaflets develop by a process of undermining or delamination of ventricular myocardium.[16] It has been suggested[17] that hemodynamic factors are important in the development of the semilunar valves,[17] and it is not unreasonable to assume that hemodynamic factors play a role in the undermining process by which the A-V valves develop. A necessary requirement for correct hemodynamic patterns of flow would be the structural integrity of the A-V canal, which is normally the narrowest orifice through which blood passes on its course from the atria to the ventricles. If an A-V canal was for some reason enlarged and was no longer the narrowest orifice of ventricular inflow, then hemodynamic forces in this area could be expected to be abnormal. If they were abnormal, proper undermining forces might no longer exist and the valve leaflets could be expected to form abnormally in both position and structure.

In our study we consistently found an abnormally large circumference of the right A-V sulcus in classic Ebstein's anomaly. This was found in hearts from patients of all ages and does not appear to be an acquired phenomenon. If this enlarged A-V junction was present at the stage when the valve leaflets were being formed, it may have been responsible for the anomalous structure and position of the leaflets. The diameter of maximal restriction to blood entering the right ventricle would no longer be at the A-V junction but would become an area of the right ventricular inflow deeper into the ventricular chamber.

Enlarged A-V junction: The reason for enlargement of the right A-V junction is elusive. One can theorize that the junction may lack proper support during development, perhaps because of a deficiency of sulcus tissue or myoepicardial mantle. However, Ebstein's anomaly is almost exclusively a disorder of the tricuspid valve, and if such a concept of lack of support is valid, why should Ebstein's anomaly not occur equally as often in the mitral valve? Odgers[15] observed several differences in the developing A-V valves, including angulation of the lateral aspect at the right A-V orifice, observed at the 30 mm stage, which was associated with temporary continuity between A-V sulcus tissue on the epicardial surface and the forming valve leaflet at the endocardial surface. This latter point is of interest because at the equivalent lateral part of the developing mitral valve, atrial and ventricular musculature separate the developing valve leaflet from the epicardially situated sulcus tissue. If sulcus tissue were deficient on the left side, the developing mitral valve could still be supported by left ventricular myocardium; however, if there were a deficiency of sulcus tissue on the right side, the lateral aspect of developing tricuspid valve would lack such

support. Lack of support could result in enlargment of the orifice followed by abnormal formation of the valve leaflets.

Conclusion

Apart from the well known downward displacement of the septal and posterior leaflets of the tricuspid valve, several other anatomic features are found consistently enough to warrant their inclusion as integral components of the congenital malformation complex of Ebstein's anomaly of the heart. These additional features include (1) malalignment, enlargement and abnormal construction of the anterior leaflet of the tricuspid valve; (2) circumferential expansion of the right A-V junction; (3) various degrees of aneurysmal dilatation of the entire right ventricle; and (4) a right to left shunt in the form of a patent foramen ovale or atrial septal defect. These anatomic characteristics should be taken into consideration in designing or carrying out the surgical correction of Ebstein's anomaly of the heart.

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Discrete Subaortic Stenosis in Newfoundland Dogs: Association Of Infective Endocarditis

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Necropsy findings are described in eight Newfoundland dogs from the same colony with discrete subaortic stenosis. Infective endocarditis involving the aortic valve occurred in four dogs and in each it proved fatal. Damage to the aortic valve cusps by the jet of blood ejected through the discretely narrowed left ventricular outflow tract predisposes to the development of infective endocarditis in both dogs and human beings with discrete subaortic stenosis. Severe abnormality of the intramural coronary arteries in the ventricular septum, which also occurs in patients with hypertrophic cardiomyopathy, was present in all eight dogs. Myocardial fiber disorganization and asymmetric septal hypertrophy, two other findings observed in patients with hypertrophic cardiomyopathy, were absent in each of the eight Newfoundland dogs with discrete subaortic stenosis.

Discrete subaortic stenosis[1–5] is not unique to man, having been described in the pig,[6] cow[7] and dog.[8] It has been studied extensively in Newfoundland dogs, in which initial breeding experiments suggest that this lesion is inherited as either a polygenic or an autosomal dominant trait with modifiers.[9] Infective endocarditis often complicates discrete subaortic stenosis in man,[5,10,11] but it has not been reported in animals with this anomaly. Recent studies in patients with tunnel subaortic stenosis indicated some similarities to hypertrophic cardiomyopathy, including myocardial fiber disorganization and abnormalities of the intramural coronary arteries.[12,13] Similar abnormalities were sought in eight Newfoundland dogs, four of which experienced infective endocarditis that proved fatal.

Animals Studied

The eight Newfoundland dogs were direct descendants from the original colony of Pyles et al.[9] Certain characteristics in these dogs are summarized in Table I. Each had a precordial systolic murmur compatible with discrete subaortic stenosis. At cardiac catheterization, at age 2 months or older, the peak systolic pressure gradient between the left ventricle and the aorta ranged from 35 to 150 mm Hg; in all but one dog this gradient was more than 60 mm Hg. The animals died at 12 to 36 months of age; three were killed and the other five died naturally, all suddenly. At necropsy, the hearts were weighed and photographed, and histologic sections were prepared. From each animal at least three sections, each measuring at least 2 cm in longest diameter and extending from the endocardium to the epicardium, were prepared for histologic study.

Results

Subaortic stenosis and infective endocarditis: The discrete subaortic narrowing was located 8 to 10 mm below the level of the most caudal extension of the aortic valve cusps (Fig. 1 to 8). The discrete narrowing was circumferential and extended transversely over the ventricular septum and the outflow surface of the anterior mitral leaflet at the level of its attachment to atrial septum. Concentric left ventricular hypertrophy (Fig. 3 to 8) occurred in all eight animals. The ventricular cavities were of normal size except in Dog 3 (Fig. 3 and 4). In-

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TABLE I

Clinical and Morphologic Observations in Newfoundland Dogs With Discrete Subaortic Stenosis

Dog no.	Age (mo) & Sex	LV-SA PSG (mm Hg)	Active Infective Endocarditis	Mechanism of Death	Heart Weight (g)	Body Weight (kg)	HW/BW Ratio*
1	12M	35	No	Killed	250	55	0.005
2	12M	150	No	Killed	450	45	0.01
3	15M	>60	No	Killed	700	50	0.01
4	18M	>60	Yes	Sudden	550	50	0.01
5	18F	>60	Yes	Sudden	520	65	0.01
6	24F	145	Yes	Sudden	400	45	0.01
7	28F	130	No	Sudden	400	45	0.01
8	36F	>60	Yes	Sudden	520	60	0.01

* The normal heart weight/body weight ratio in adult Newfoundland dogs without heart disease is not available. This ratio is available in beagles, and it is approximately 0.008. Beagles, however, weigh only up to 15 kg, whereas adult Newfoundland dogs generally weigh between 45 and 70 kg. We therefore believe that the normal heart weight/body weight ratio in adult Newfoundland dogs is somewhat lower than in beagles and is probably about 0.005.

BW = body weight; HW = heart weight; LV = left ventricle; PSG = peak systolic gradient; SA = systemic artery.

fective endocarditis occurred in four of five dogs that died spontaneously (Fig. 5, 7 and 8) but in none of the three killed dogs. In three of the four dogs with infection, vegetations partially obstructed the ostium of the left coronary artery. One or more perforations were present in one or more cusps of the aortic valve in each of the four dogs with infective endocarditis. The infective process also involved the subaortic membrane and the ventricular aspect of the anterior mitral leaflet in two dogs (Fig. 6). Focal necrosis of the left ventricular papillary muscle also occurred in each of the four dogs with infective endocarditis. Large colonies of gram-positive cocci, inflammatory cells (mainly polymorphonuclear leukocytes) and necrotic cell debris were observed histologically in the vegetations in all four dogs. Microabscesses also occurred in the left ventricular myocardium in all four dogs.

Coronary arterial abnormalities: Luminal narrowing, intimal fibrous proliferation, medial hypertrophy and medial smooth muscle disorganization were noted in many intramural coronary arteries in the ventricular septum in all eight dogs (Fig. 2 to 6). In contrast, the extramural branches of the coronary arteries were normal and free of emboli or thrombi. Septic emboli, however, were found in one or more intramural coronary arteries of three dogs with infective endocarditis. Foci of myocardial fiber disorganization, of the kind observed in patients with hypertrophic cardiomyopathy, were not noted in the ventricular septum in any of the eight dogs.

Comments

Mechanism of infective endocarditis: That infective endocarditis develops after damage to the endothelial covering of the aortic valve cusps by blood ejected through the subaortic discrete obstruction under high pressure and velocity is in agreement with the findings in experimental animal models of endocarditis.[14] Endothelial cells can be detached from the vascular surface by mechanical forces generated by a jet of blood.[15,16] Furthermore, denudation of endothelium exposes the subendothelial space, which is covered by a layer of fibrin.[14] Bacteria circulating in the bloodstream adhere to the fibrin deposits. Thus, endothelial damage appears to be an important event in the development of infective endocarditis.

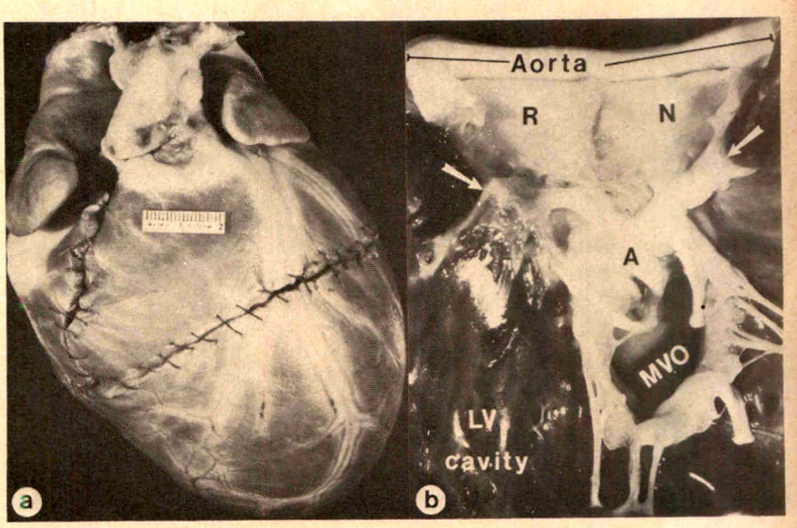


FIGURE 1. Dog 2. **a**, exterior view of heart showing a very large left ventricle. **b**, opened left ventricular (LV) outflow tract showing the discrete "membrane" **(between arrows).** The peak systolic pressure gradient between the left ventricle and the systemic artery was 150 mm Hg. A = anterior mitral leaflet; MVO = mitral valve orifice; N = noncoronary and R = right aortic valve cusps.

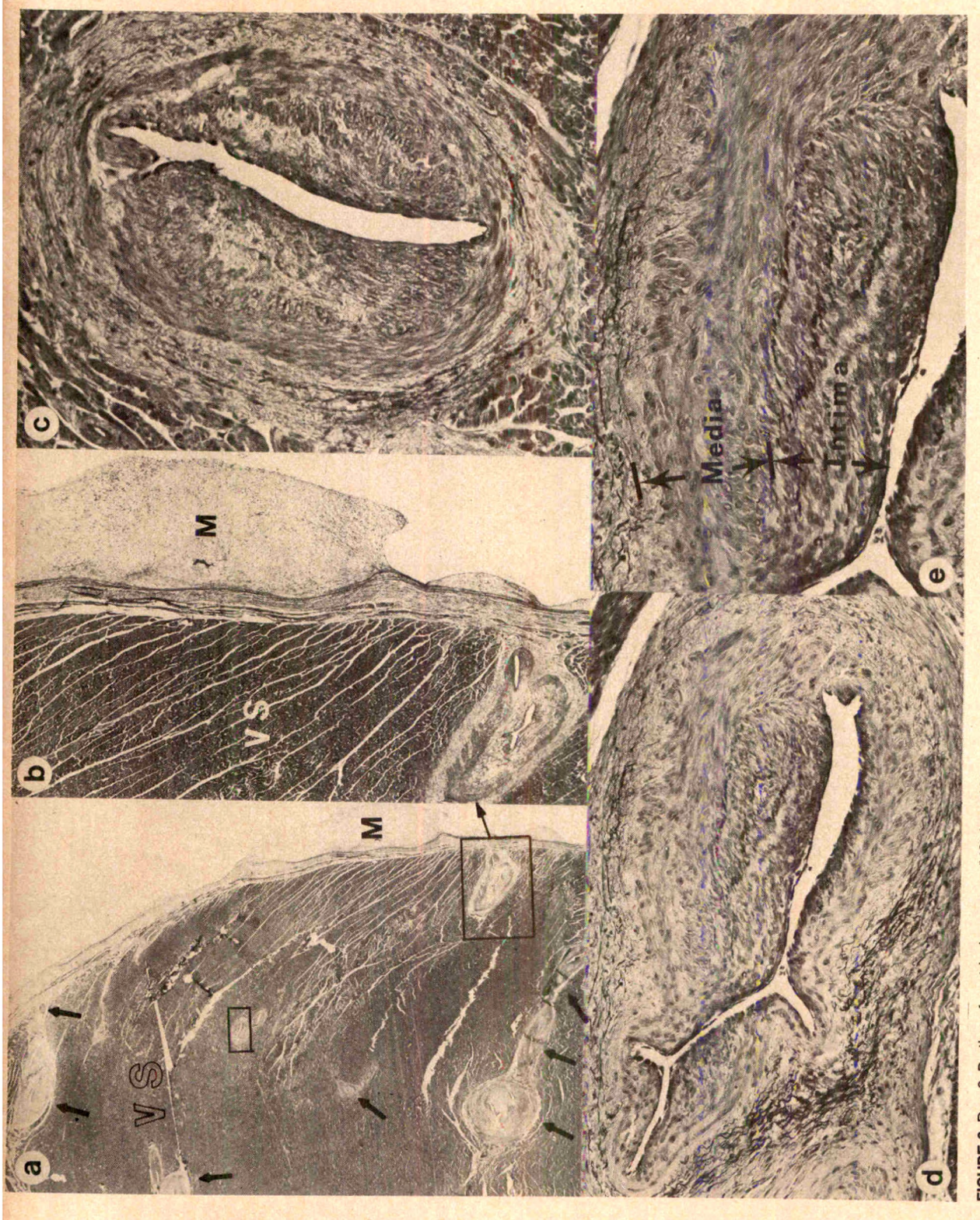


FIGURE 2. Dog 2. Portion of ventricular septum (VS) (**a** and **b**) showing several intramural coronary arteries. **a**, several intramural coronary arteries are designated by either **arrows** or **rectangles.** M = "membrane" of the discrete subaortic stenosis in the left ventricular outflow tract. **b**, a closer view of an area shown in **a**. VS = ventricular septum. **c**, an intramural coronary artery shown in the **rectangle** in **a. d,** another intramural coronary artery, and (**e**) a close-up view of a portion of its wall. (Movat stains ×10 [**a**], ×27 [**b**], ×220 [**c**], ×130 [**d**] and ×250 [**e**], all reduced by 7 percent.)

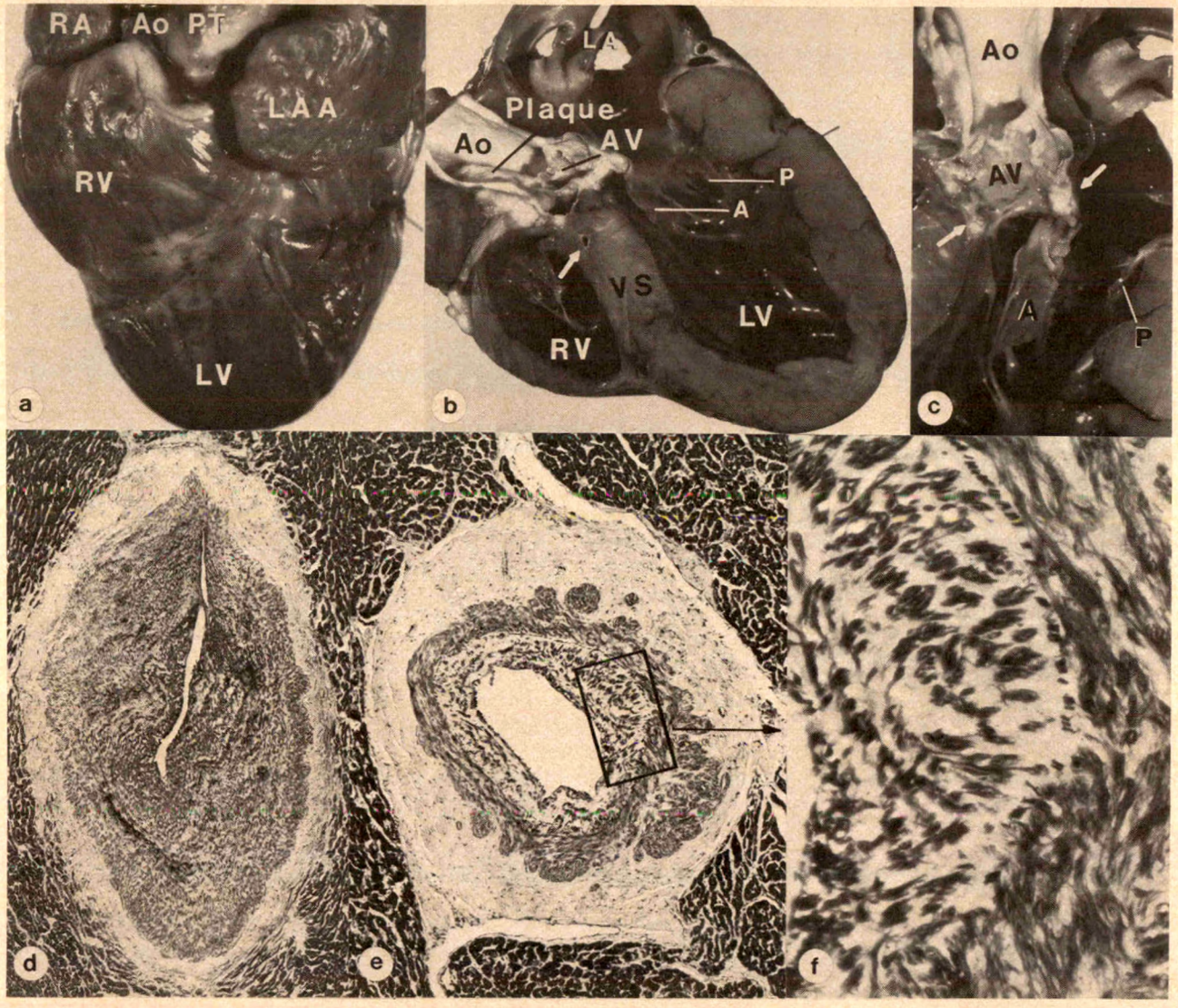


FIGURE 3. Dog 3. Heart **(a, b, c)** and intramural coronary arteries in ventricular septum (VS) **(d, e, f). a,** exterior view showing a very large left ventricle (LV) and left atrial appendage (LAA). Ao = ascending aorta; PT = pulmonary trunk; RA = right atrium; RV = right ventricle. **b,** view after removing the anterior half. The left ventricle is dilated. This was the only dog with a dilated left ventricle. The subaortic membrane is located **between the arrows** in the left ventricular outflow tract shown in **c.** The aortic valve (AV) cusps are thickened by fibrous tissue, and the intima in the ascending aorta is focally thickened. A large coronary artery **(white arrow in b)** is present in the cephalad portion of the ventricular septum. A = anterior and P = posterior mitral leaflets; LA = left atrium. **d** and **e,** intramural coronary arteries in ventricular septum. The internal elastic membrane is not discernible in **d,** but it is preserved in **e.** A close-up view of a portion of wall of the artery in **e** is shown in **f.** The cells in the intima are arranged primarily perpendicular to the lining of the lumen. In contrast, the cells in the media are arranged more or less parallel to the lining of the lumen. The cells with spindle- or strap-shapes are considered smooth muscle cells. (Movat stains ×54 [**d**], ×80 [**e**] and ×380 [**f**], all reduced by 18 percent.)

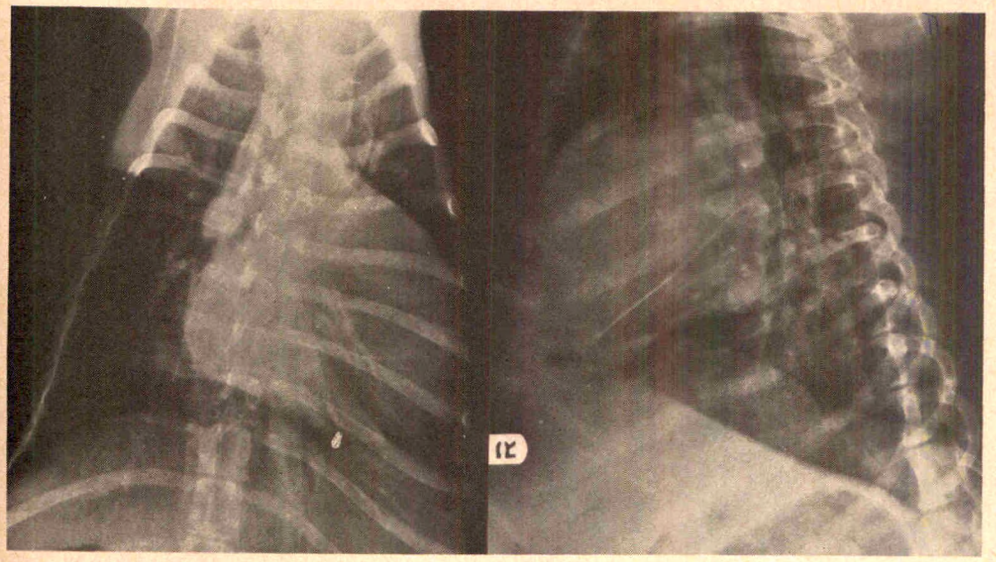


FIGURE 4. Dog 3. Radiographs of heart showing massive cardiomegaly. **Left,** posteroanterior view; **right,** lateral view.

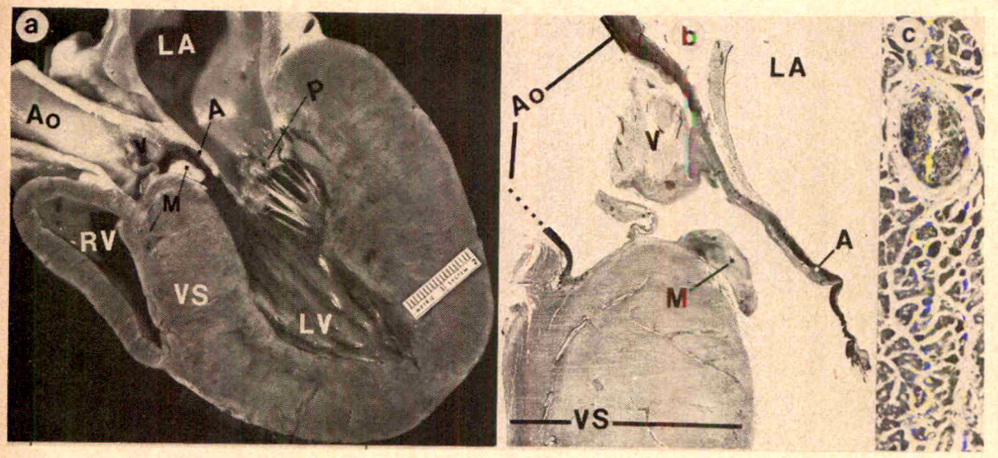


FIGURE 5. Dog 4. **a**, heart in longitudinal view. **b**, photomicrograph of left ventricular outflow tract showing a vegetation (V) occupying much of one sinus of Valsalva. **c**, narrowed intramural coronary artery in ventricular septum. Abbreviations as in previous figures. (Movat stains ×5 [**b**] and ×140 [**c**], both reduced by 34 percent.)

TABLE II

Infective Endocarditis (IE) in Patients with Discrete Subaortic Stenosis (DSS): Summary of Previously Reported Cases

Reference		Patients With DSS	Patients With IE	
First Author	Year	(no.)	no.	%
Nonnecropsy Patients or Clinical Studies				
Brock[17]	1959	16	0	0
Braunwald[1]	1963	20	0	0
Morrow[10]	1965	4	4	100
Campbell[2]	1968	7	0	0
McGoon[3]	1969	30	1*	3
Reis[18]	1971	21	2	10
Shariatzadeh[19]	1972	20	0	0
Kelly[20]	1972	25	0	0
Champsaur[21]	1973	20	0	0
Popp[22]	1974	3	1	33
Mody[23]	1975	6	0	0
Wyman[24]	1976	70	0	0
Newfeld[25]	1976	51	1	2
Chiariello[4]	1976	11	0	0
Necropsy Patients				
Fontana[11]	1962	29	13	45
Roberts[5]	1973	7	4	57

* IE after operation only.

Incidence of infective endocarditis in subaortic stenosis: The frequency of infective endocarditis in animals with discrete subaortic stenosis is not known. Reports of infective endocarditis in patients with discrete subaortic stenosis are summarized in Table II.[1–5,10,17–25] The frequency of infective endocarditis in patients with discrete subaortic stenosis was 45 percent in the 29 necropsy cases collected by Fontana and Edwards from previous reports.[11] This is the highest reported incidence rate of infective endocarditis associated with any congenital or acquired cardiac disorder. Of the seven patients with discrete subaortic stenosis we studied at necropsy (Table I), four had infective endocarditis[5] that was active in two and healed in two. Lower frequencies of infective endocarditis have been reported in other series of patients with discrete subaortic stenosis. The much lower frequency (less than 10 percent) (Table II) of infective endocarditis in the clinical reports of discrete subaortic stenosis may be due in part to early operative treatment (before aortic valve scarring or infection occurred).

Clinical and hemodynamic consequences of infective endocarditis: When infective endocarditis does

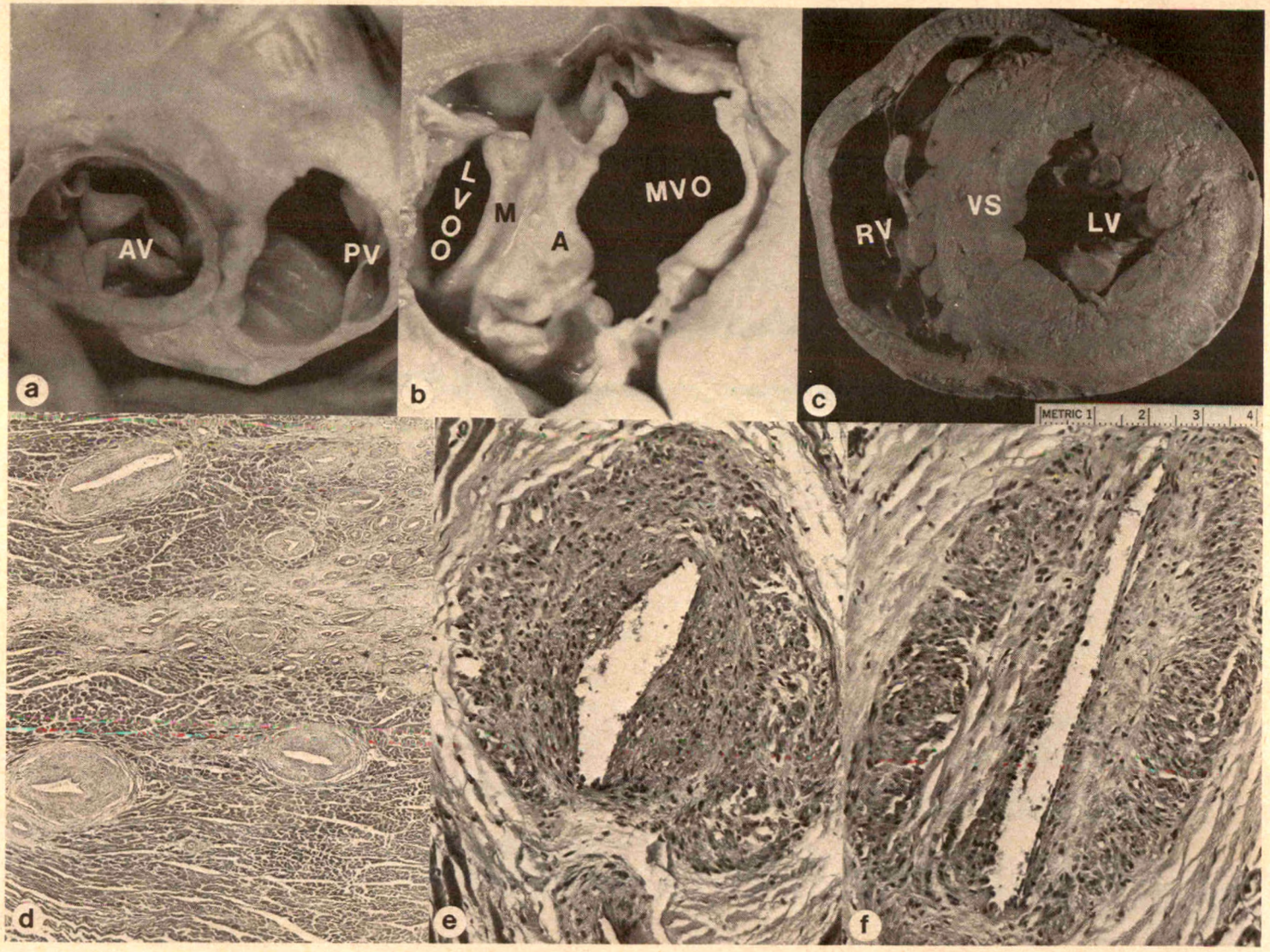


FIGURE 6. Dog 7. Heart **(a, b, c)** and intramural coronary arteries of ventricular septum **(d, e, f). a,** aortic valve (AV) and pulmonary valve (PV) from above. The aortic valve cusps are thick whereas the pulmonary valve cusps are normal. **b**, left ventricular outflow tract as viewed from the left ventricle. The left ventricular outflow obstruction (LVOO) is produced by the subaortic membrane (M), which is attached to the anterior mitral leaflet (A) as well as to the mural endocardium (poorly shown). This dog had a high (130 mm Hg) peak systolic pressure gradient between the left ventricle and the systemic artery. MVO = mitral valve orifice. **c**, transverse section of the ventricles showing symmetric hypertrophy. LV = left ventricle; RV = right ventricle; VS = ventricular septum. **d**, several intramural coronary vessels in the ventricular septum. Most of them have narrowed lumens. The largest diameter of the lumens tends to be similarly oriented in most of the arteries. Replacement myocardial fibrosis also is present. **e** and **f**, close-up views of two arteries. The internal elastic membranes are not distinct. (Movat stains ×40 [**d**], ×330 [**e**] and ×220 [**f**], all reduced by 13 percent.)

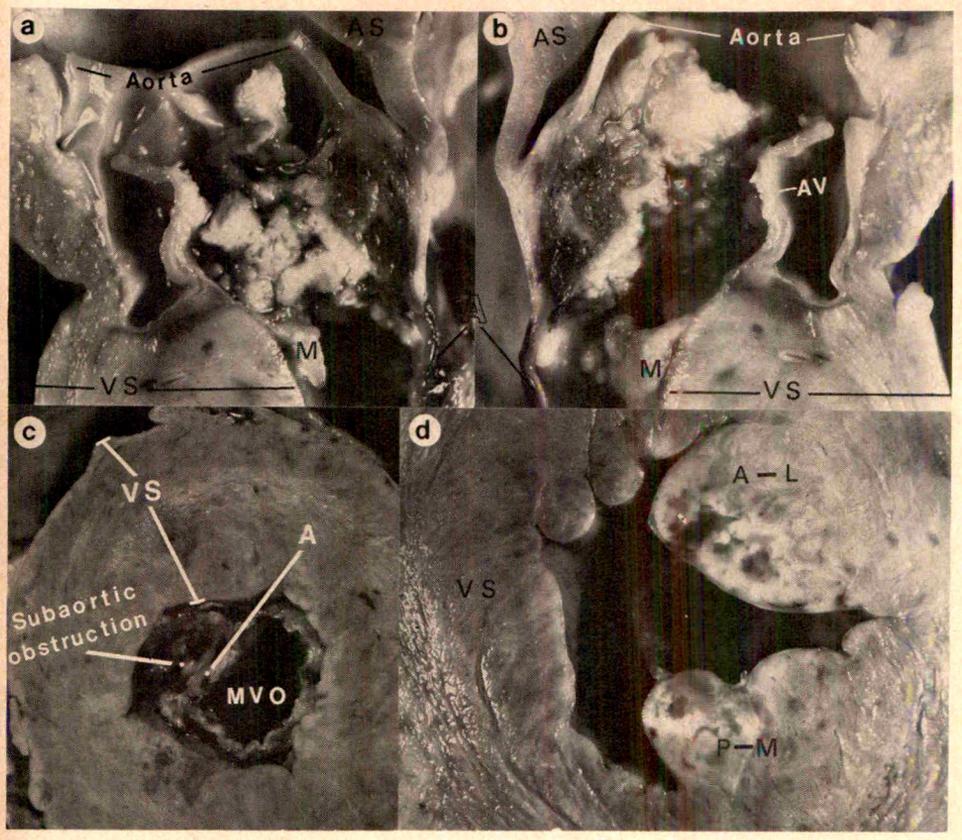


FIGURE 7. Dog 6. Heart with infective endocarditis. A peak systolic pressure gradient between the left ventricle and the systemic artery of 145 mm Hg was measured earlier in life before the cardiac infection occurred. **a**, view of posterior half of the heart as seen anteriorly showing the infected aortic valve. A = anterior mitral leaflet; AS = atrial septum; M = subaortic "membrane"; VS = ventricular septum. **b**, similar anatomy but a view of the anterior half of the aortic valve (AV) as seen posteriorly. The vegetative material has extended to involve the subaortic membrane. A large intramural coronary artery is present in the ventricular septum. **c**, view of subaortic obstruction from below. MVO = mitral valve orifice. **d**, close-up view of the anterolateral (A-L) and posteromedial (P-M) papillary muscles showing extensive necrosis of each.

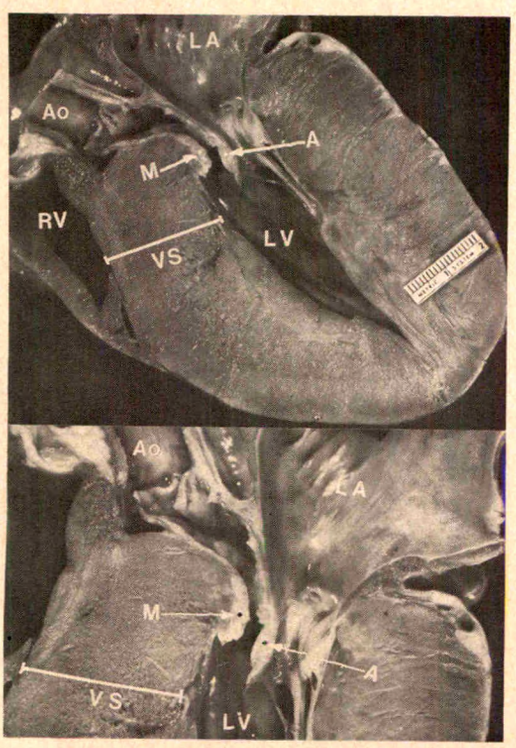


FIGURE 8. Dog 8. Heart with infective endocarditis on the aortic valve. Here, however, the vegetations are not discernible but the aortic valve cusps and subaortic obstruction (due to the close apposition of the "membrane" [M] and the anterior [A] mitral leaflet) are clearly seen. Abbreviations as in previous legends.

complicate discrete subaortic stenosis, clinical manifestations of aortic valve damage may be entirely absent, in contrast to their near universal occurrence in patients with infective endocarditis of the aortic valve and no subaortic obstruction. Damage to the aortic valve from infection in patients without subaortic stenosis generally leads to severe aortic regurgitation, progressive dilatation of the left ventricle and, finally, overt congestive heart failure. In patients with subaortic stenosis, the subaortic obstruction prevents severe aortic regurgitation from occurring because the subvalve chamber above the subaortic obstruction is too small to accommodate much regurgitant volume. As a consequence, diagnosis of infective endocarditis in patients with discrete subaortic stenosis may be unduly delayed. Also, in patients with infective endocarditis of the aortic valve without subaortic stenosis, the hemodynamic consequence is *pure* aortic regurgitation. In contrast, in the person or dog with infective endocarditis of the aortic valve and subaortic stenosis, the vegetations may extend onto the subaortic "membrane" and cause further obstruction to left ventricular outflow. In all four Newfoundland dogs with infective endocarditis, death was sudden and in each the left ventricular outflow obstruction appeared to have been worsened by the vegetations.

Intramural coronary arterial abnormalities: Severe abnormality of the intramural coronary arteries of the ventricular septum occurred in each of the eight

dogs. These abnormalities consisted of considerable increase in vessel size, intimal smooth muscle proliferation, medial hypertrophy, disorganization of the media with loss or absence of the internal elastic membrane and luminal narrowing. In addition, the number of intramural coronary arteries in the septum appeared to be increased. These abnormalities were minimal or absent in the left and right ventricular free walls. Similar changes in intramural coronary arteries of dogs with discrete subaortic stenosis were described by Flickinger and Patterson.[26] These changes in intramural coronary arteries are identical to those observed in about half of patients with hypertrophic cardiomyopathy studied at necropsy.[12] The cause of the changes in the intramural coronary arteries is uncertain, but these changes, together with those in patients with hypertrophic cardiomyopathy,[12] are the most impressive changes we have observed in the intramural coronary arteries in any condition. The changes appeared just as extreme in the 12 month old animal as in the 36 month old animal; however, study of eight newborn Newfoundland puppies from the same colony as the eight dogs described here disclosed no abnormalities of the intramural coronary arteries. Similar abnormalities of the intramural coronary arteries in the ventricular septum were also observed in four patients with discrete subaortic stenosis whom we studied at necropsy with histologic examination of the ventricular septum (Roberts WC, unpublished observations).

Coronary blood flow: Although the cause or causes of the alterations in the intramural coronary arteries in our Newfoundland dogs are uncertain, abnormalities in coronary blood flow may be important. Pyle et al.[27] showed in both German shepherd and Newfoundland dogs with discrete subaortic stenosis that flow of blood in the left coronary arteries is diminished and that it is reversed during most of ventricular systole both at rest and during exercise. Significant retrograde flow during any portion of systole has never been observed in the normal dog.[28]

Whether coronary blood flow is abnormal in patients with left ventricular outflow obstruction and morphologically abnormal intramural coronary arteries is uncertain. In human beings, abnormal intramural coronary arteries, particularly those in the ventricular system, were observed in hypertrophic cardiomyopathy,[12] in discrete subaortic stenosis (Roberts WC, unpublished observations) and in tunnel subaortic stenosis,[13] but not in aortic valve stenosis.[12] In the latter condition, the obstruction is usually acquired later in life, whereas in the other three conditions it is present from birth or at least in early life. Early onset of obstruction may be essential for development of the abnormalities in the intramural coronary arteries.

Discrete subaortic stenosis versus hypertrophic cardiomyopathy: Although the alterations we described in the intramural coronary arteries in the ventricular septum suggest a similarity between discrete subaortic stenosis and hypertrophic cardiomyopathy, both dogs and human beings with discrete subaortic stenosis have concentric left ventricular hypertrophy rather than asymmetric septal hypertrophy; and myocardial fiber disorientation in the ventricular septum, as observed in patients with hypertrophic cardiomyopathy,[29] is absent in both dogs and patients with discrete subaortic stenosis. Thus, discrete subaortic stenosis and hypertrophic cardiomyopathy are distinctly separate entities.

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Pathogenesis of Persistent Truncus Arteriosus in Light of Observations Made in a Dog Embryo With the Anomaly

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Among 36 embryos obtained from a strain of Keeshond dogs in which there is a large incidence of spontaneously occurring conotruncal anomalies, a specimen with persistent truncus arteriosus, type 1 was found. The embryo had a crown-rump length of 20 mm. The specimen was serially sectioned and a wax plate reconstruction was made of the heart and proximal great vessels at a magnification of ×100. The truncal valve was quadricuspid and dysplastic; associated anomalies were a right subclavian artery arising anomalously from the descending aorta, a single coronary artery, an absent ductus arteriosus and a small persistent left cranial (superior) vena cava. The truncus cushions were hypoplastic, had failed to fuse and each had simply produced an arterial cusp.

The observations made on this embryo support the view that in persistent truncus arteriosus there is failure of septation of the truncus arteriosus. No evidence was found in favor of the concept that persistent truncus arteriosus represents a form of tetralogy of Fallot with atresia of the subpulmonary infundibulum and partial or complete absence of the aorticopulmonary septum.

The cardiac anomaly known as persistent truncus arteriosus, although not common, has evoked great interest since the first well documented case was reported by Wilson[1] in 1798. A major reason for this interest may be related to the apparent ease with which the anomaly can be "explained" as persistence of an early embryonic condition as a result of failure of septation of the arterial pole of the heart. This concept of the pathogenesis of the anomaly, embodied in the titles of even such early publications as those by Buchanan[2] and Pitschel,[3] has been widely accepted. However, some differences of opinion have continued to exist about both the pathogenesis of the defect[4–7] and the specific anatomic features of an anomalous heart that make it a bona fide example of persistent truncus arteriosus.[5–10] These disagreements have been of a relatively minor nature and can generally be ascribed to the fact that until recently important details concerning development of the heart and the aortic arch systems were imperfectly known.

The older concept of a bulbar (truncoconal) septum, which begins as a spur appearing between the origins of the fourth and sixth embryonic aortic arches and then grows proximally in a spiral fashion preceded by bulbar (truncoconal) ridges, is now known to represent an oversimplification. It has led to difficulties in classification, improper use of the term truncus arteriosus communis, misconceptions as to the nature and pathogenesis of lesions such as aorticopulmonary window (aorticopulmonary septal defect) and persistent truncus arteriosus, type 4 of Collett and Edwards,[9] and the creation of the unfortunate terms "partial" and "complete" forms of persistent truncus arteriosus.[6–8]

Humphreys[8] defined persistent truncus arteriosus as the condition in which a single arterial trunk gives off the coronary arteries, the sys-

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temic arteries and the blood supply to the lungs, either through pulmonary arteries or, if the sixth arches do not develop, by means of collateral vessels. A ventricular septal defect is always present. The trunk arises either from the right ventricle or overrides the ventricular septal defect, and the crista supraventricularis, if present, should stop beneath the common ostium.

Hülse[5] and others emphasized that ideally a quadricuspid valve with coronary arteries arising from opposite sinuses of Valsalva should be present to make a positive diagnosis. However, he conceded that abnormal numbers of cusps may occur as associated primary anomalies. Humphreys[8] also thought that on theoretical grounds four cusps might be expected but realized that this condition cannot always be insisted upon. She also pointed out the difficulty of distinguishing persistent truncus arteriosus from solitary aortic trunk when remnants of sixth arch derivatives cannot be found.

Lev and Saphir[11] believed that the single criterion necessary for the diagnosis is the presence of only one large trunk emanating from the heart which gives off the coronary arteries, the pulmonary arteries and the systemic arteries. They agreed with Humphreys[8] that the number of semilunar valves is not a primary criterion.

Collett and Edwards,[9] in their classic paper, mainly followed Humphreys' definition and proposed a classification of persistent truncus arteriosus that has had wide usage. In their type 1, by far the most common variant, the two pulmonary arteries have a short common stem originating from the trunk. In the less common type 2, they arise independently from the trunk but close together, and in the rare type 3 they are more or less widely separated. In type 4 the lungs are supplied by vessels arising from the descending aorta or by bronchial arterial collateral channels. It is difficult to differentiate type 4 from the extreme forms of tetralogy of Fallot in which the pulmonary trunk is reduced to a hard-to-find fibrous strand, and in many cases initially believed to be persistent truncus arteriosus type 4, the latter is found on careful macroscopic and even microscopic[10,12] reexamination. Because of this difficulty there has been a tendency recently to reject type 4 as a variant of persistent truncus arteriosus.[10,13,15] Some authors have lumped types 2 and 3 together as a single variant.[13–15]

In 1965 Van Praagh and Van Praagh,[13] on the basis of 57 cases of persistent truncus arteriosus, reclassified the anomaly and expressed views on its nature and pathogenesis that represent a radical departure from those held previously. Two basic types of persistent truncus arteriosus were distinguished, each with several subtypes: those with (type A) and those without (type B) a ventricular septal defect. Type A corresponds to persistent truncus arteriosus in the classic sense. Type B is characterized by two well developed arterial valves and represents a condition usually considered a form of aorticopulmonary septal defect. Van Praagh and Van Praagh[13] stated that there is "no such thing as 'true' persistent truncus arteriosus in the time-honored sense of persistence of an undivided conotruncal channel." They also stated that "in essence truncus with a ventricular septal defect is tetralogy of Fallot with pulmonary atresia, plus partial or complete absence of the aorticopulmonary septum." According to these authors, the distal pulmonary infundibulum, in fact the entire "distal conus," is absent, as is part or all of the aorticopulmonary septum.

The single arterial valve, if tricuspid, is considered to be the aortic valve. A quadricuspid valve is believed to be the aortic valve plus a remnant of the pulmonary valve. In a more recent paper by Calder et al.,[16] the concept was modified somewhat and typical truncus arteriosus communis was "thought to result from atresia rather than absence of the subpulmonary infundibulum, with partial or complete absence of the pulmonary valve and an aorticopulmonary septal defect." The reason for the modification, explained in an editorial reply by Van Praagh[17] to an editorial comment by Edwards[18] in relation to this paper, is that if the subpulmonary infundibulum were absent the pulmonary valve would be well formed rather than partially or totally absent.

In a recent study of embryologic material obtained from a strain of purebred Keeshond dogs in which conotruncal anomalies occur spontaneously in a large percent of cases,[19,20] we encountered an embryo of 20 mm crown-rump length (Streeter's horizon[21] or stage XX) with what is usually referred to as persistent truncus arteriosus type 1 of Collett and Edwards.[9] Normally, at this stage of development the cardiac septa have been completed, but the various components that make up these septa and, more specifically, those that form the conotruncal septum, can still be recognized easily. The pathogenesis of persistent truncus arteriosus is clearly demonstrated, particularly if the observations made in the specimen are considered within the framework of the spectrum of conotruncal anomalies that occur in this particular strain of dogs, of which persistent truncus arteriosus appears to represent the extreme form.[20]

We know of only two other embryos with persistent truncus arteriosus, type 1 that have been described—a 25 mm pig embryo described by Shaner[22] and a stage XXII human embryo described by Maron and Hutchins.[23]

Material and Methods

Details concerning the methods used to study the pathology and pathogenesis of the conotruncal anomalies in the dog have previously been given.[20] Embryos were obtained by hysterectomy and immediately fixed and partly dehydrated in Carnoy's solution. Dehydration was completed in three changes of 100 percent ethanol and two changes of methyl benzoate. The specimens were then carried through two changes of benzene and embedded in Paraplast.® Transverse serial sections were made at 10 or 20 μ and stained with Mayer's hematoxylin, phloxin and saffron. Wax plate reconstructions at ×100 enlargement were made according to the method originally described by Born[24] and recently modified by Sack,[25] using every section.

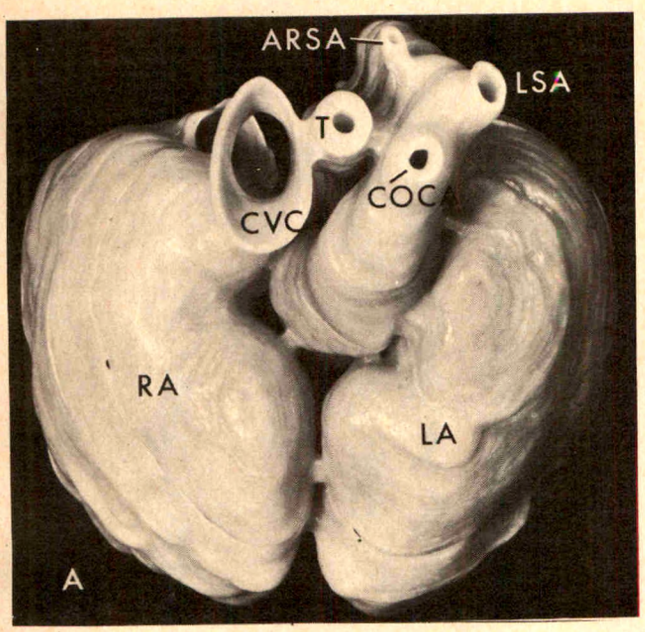
A small (×50) solid preliminary model was made of the heart and the aortic arch system of a normal embryo. To assure accurate reconstruction of the heart, that is, proper stacking of the wax cutouts of the heart sections, the following procedures were followed: (1) The plane of sectioning was

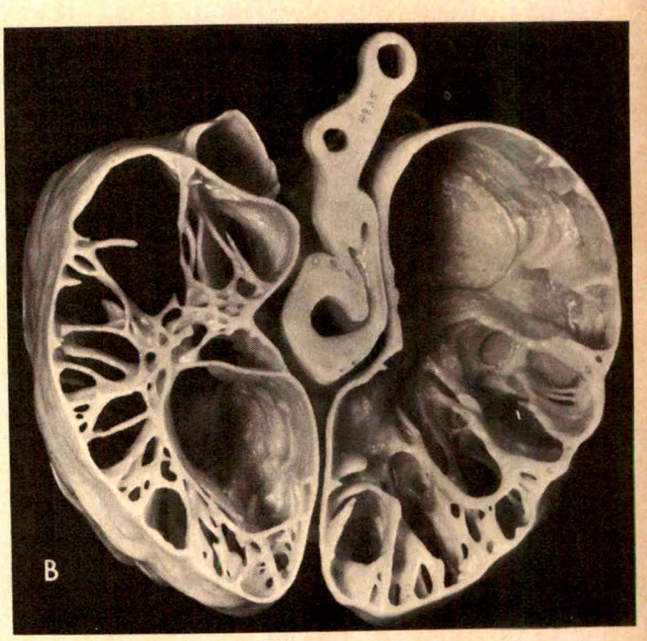
made to be perpendicular to the back of the embryo which, in specimens of stage XX, is nearly straight at the level of the heart. (2) A line was scratched lightly in the wax plate connecting the projected image of the center of the neural canal and the tiny remnant of the notochord. This line was carried anteriorly through the image of the heart section and, where it intersected with the anterior and posterior borders of the heart, was carried through the full thickness of the wax plate. This, after the heart section had been cut out, produced notches anteriorly and posteriorly that were lined up in stacking the cutouts, ensuring accuracy in the sagittal plane. (3) A small hole was made with a hot needle in every cutout along the scratch a certain distance anterior to the notochord. This distance was chosen so that the hole was located near the center of the cutout of the heart. Because the spinal column and the notochord are nearly straight, lining up the hole made it possible to stack the wax plate cutouts with reasonable accuracy in the frontal plane. The irregular shapes of the heart and great vessel sections further aided in this. (4) Accuracy of reconstruction was checked by comparing the model with a dissected heart of an embryo of the same age, usually a littermate.

A second model of the same heart was then made at the larger magnification. This time the interior, including as many of the trabeculae as possible, was also reconstructed. The cutouts were stacked using the small preliminary model as a guide. The complexity of the trabecular pattern was very helpful in further refining the accuracy of the reconstructions. In preparing reconstructions of pathologic specimens the normal models were used as guides.

Description of the Embryo

The litter: The embryo with persistent truncus arteriosus was one of a litter of six, all members of which had cardiovascular anomalies.[20] The sire had a large ventricular septal defect, dextroposition of the aorta and severe pulmonary valve





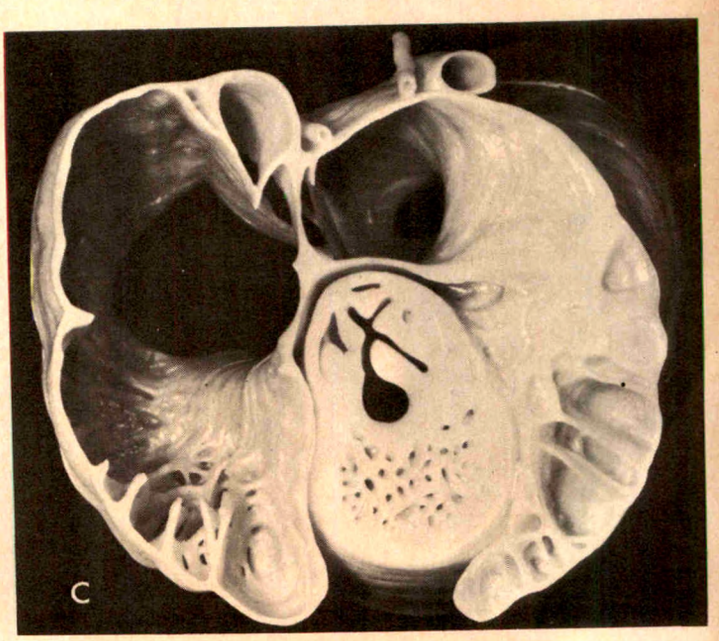


FIGURE 1. Wax plate reconstruction of dog embryo heart with persistent truncus arteriosus, type 1. **A,** top view of model; **B,** at level of origin of pulmonary trunk; **C,** at level of truncal valve. ARSA = anomalous right subclavian artery; COCA = common origin of carotid arteries; CVC = cranial (superior) vena cava; LA = left atrium; LSA = left subclavian artery; RA = right atrium; T = trachea.

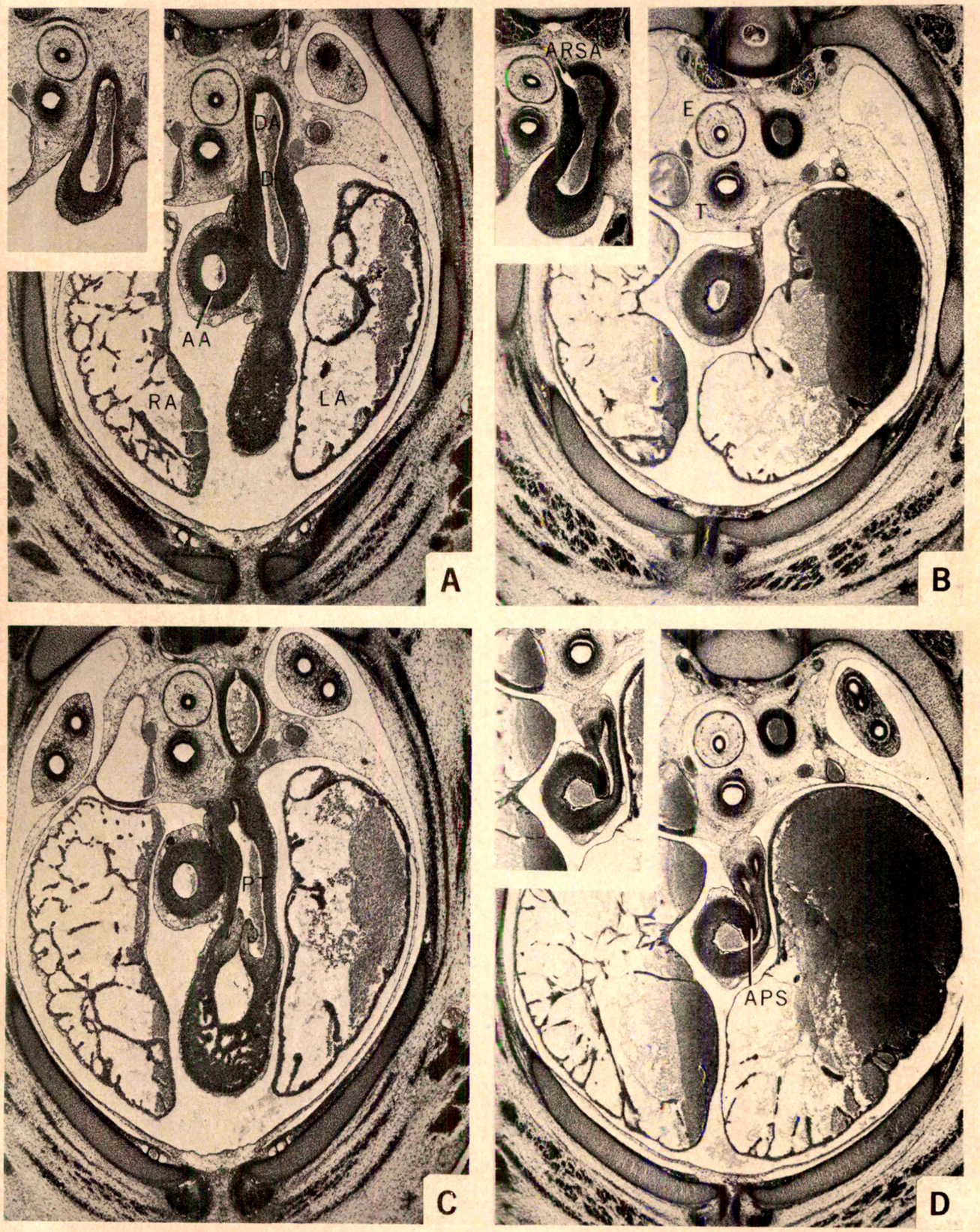
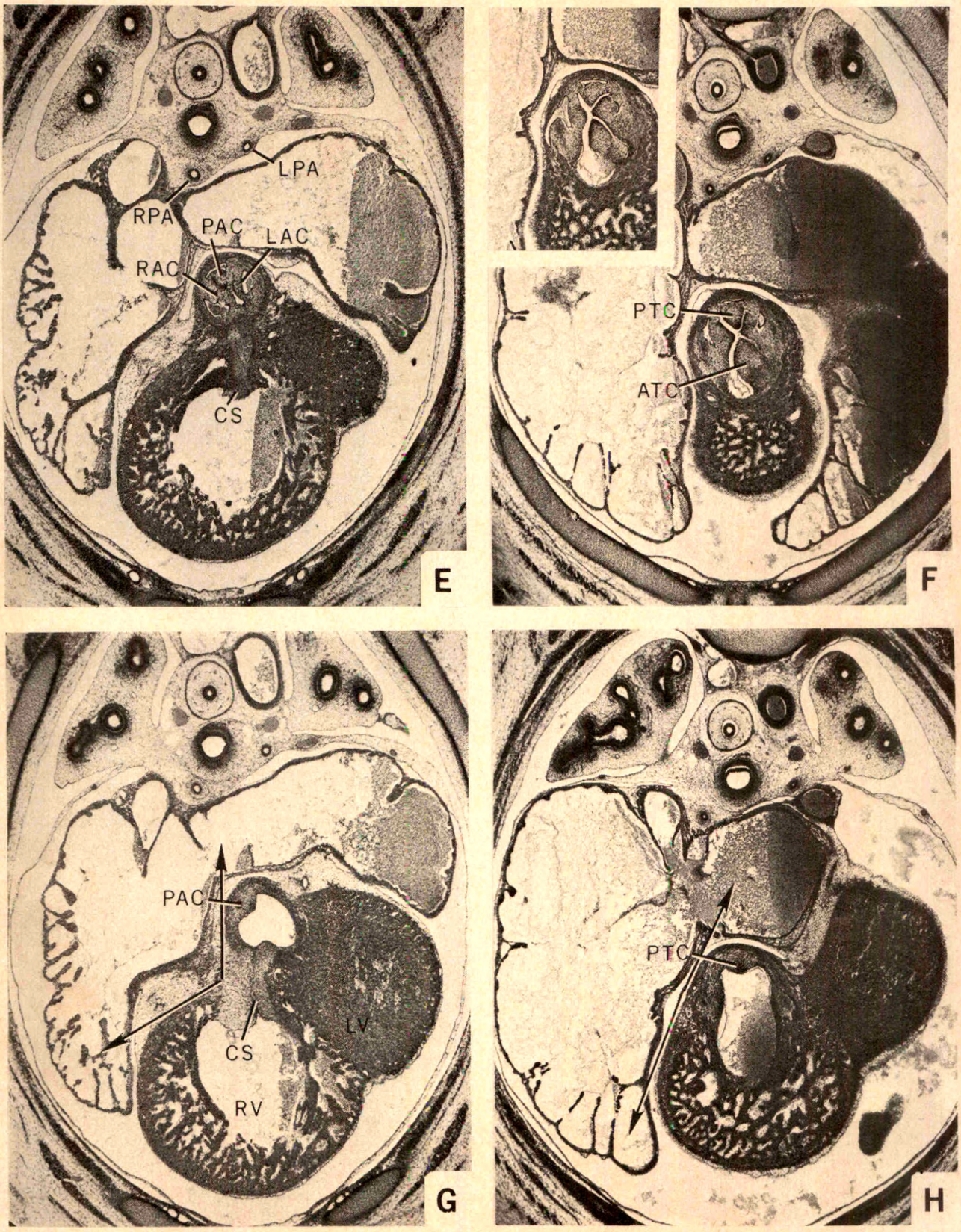


FIGURE 2. Selected transverse sections. **A,C,E** and **G,** Normal embryo of stage XX (no. 44056B). **B,D,F,H,** specimen with persistant truncus arteriosus (no. 4835). **A,** and **B,** level of ductus arteriosus, absent in **B. Insert,** level of aortic arch. **C,** and **D.** level of pulmonary trunk. Insert, one section higher. **E** and **F,** level of aortic (truncal) valve. Insert, origin of single coronary artery. **G** and **H,** level of conal septum. Conus cushions are diminutive in **H.** Compare the position of the posterior (noncoronary) cusps. Compare also the angle subtended by the **arrows** in **G** with the corresponding angle



in **H.** AA = ascending aorta; APS = aorticopulmonary septum; ATC = anterior truncal valve cusp; CS = conal septum; D = ductus arteriosus; DA = descending aorta; E = esophagus; L(R)AC = left (right) aortic valve cusp; L(R)PA = left (right) pulmonary artery; L(R)TC = left (right) truncal valve cusp; L(R)V = left (right) ventricle; PAC = posterior aortic valve cusp; PT = pulmonary trunk; PTC = posterior truncal valve cusp. Other abbreviations as before.

stenosis. The dam had a ventricular septal defect and a patent ductus arteriosus. Five of the embryos had a ventricular septal defect, which was small in one, moderately large in two and very large in the remaining two. In the latter two specimens there was a marked dextroposition of the aorta. One specimen had a dysplastic pulmonary valve and a ventricular septal defect of moderate size and another specimen had a persistent left superior vena cava and a large ventricular septal defect. Three specimens had a right subclavian artery arising anomalously from the descending aorta.

The heart of the sixth embryo (Fig. 1 and 2): This heart also had a small persistent left superior vena cava, but otherwise the systemic veins, the atria and the atrial septum were normal. The right atrioventricular (tricuspid) valve and the body of the right ventricle were normal for an embryo of stage XX. A medial papillary muscle is not yet present at this stage.[20] There was a very large basilar ventricular septal defect, and the single arterial trunk present in this heart arose almost exclusively from the right ventricle. There was no conal septum. Both conal cushions were very small (Fig. 2H). The truncal cushions also were small and had not fused, and therefore the truncus arteriosus was undivided (Fig. 2F). Each of the truncal cushions was approximately equal in size to the normally formed intercalated valve cushions and was in the process of forming a single cusp. Therefore, the single arterial valve present was quadricuspid, with anterior and posterior cusps formed respectively by the pulmonary and aortic intercalated valve cushions, and right and left cusps produced by the hypoplastic truncus cushions. All four cusps were thicker than those of the arterial valves in normal dog embryos of the same age (Fig. 2, C, E, F).

A single coronary artery arose from the right sinus of Valsalva (Fig. 1C and 2F) and divided into two branches. The first of these pursued a course similar to that of a normal right coronary artery. The second crossed the right ventricular outflow tract to the left and, upon reaching the anterior interventricular groove, bifurcated into left anterior descending and circumflex arteries.

A short narrow pulmonary trunk arose from the left side of the single arterial trunk and bifurcated into right and left pulmonary arteries (Fig. 2D). There was no trace of a ductus arteriosus (Fig. 2B), and the left recurrent laryngeal nerve ran underneath the aortic arch. The aortic arch was on the left side and its first branch was the bicarotid trunk (common origin of the two carotid arteries, Fig. 1A), followed by the left subclavian artery. The right subclavian artery arose anomalously from the descending portion of the aortic arch (Fig. 2B). It then coursed behind the esophagus and ascended to reach the right forelimb. The pulmonary veins, left atrium, left atrioventricular (mitral) valve and left ventricle were normal.

Interpretation of the Specimen

Anomalies of the ventricular outflow tract in the Keeshond dog: The spectrum of anomalies involving the ventricular outflow tract of the heart in the Keeshond dog family ranges from an absent medial papillary muscle and persistence of a conal septal fusion line to a large basilar ventricular septal defect with pronounced dextroposition of the aorta, with or without dysplasia or stenosis of the pulmonary valve, or both.[19] Embryologic studies clearly demonstrated that the primary anomaly is a varying degree of hypoplasia of the conal cushions involving only their proximal part in the milder cases.[20] Increasing distal involvement of the conal cushions, eventually also involving the proximal truncal cushions, results in a ventricular septal defect of increasing size, a hypoplastic or absent conal septum (infundibular septum in the postnatal heart) and an increasing degree of aortic dextroposition. In the more severe forms the aorta arises almost exclusively from the right ventricle and, in some instances with associated pulmonary stenosis or atresia, the ductus arteriosus is absent.[19,20]

Persistent truncus arteriosus—an extreme form of hypoplasia of the truncal and often also of the conal cushions: We believe that the specimen described here represents the extreme form of the anomaly. The conal cushions are very small and the conal septum is therefore absent. Eventually this would have led to an absent infundibular septum as in most human cases of persistent truncus arteriosus. However, in a minority of specimens in man there is a muscular band, sometimes quite well developed, that separates the tricuspid from the truncal valve and that may have a normal medial papillary muscle. We believe that in such cases the conal septum, and therefore the infundibular septum of the postnatal heart, has formed. The interventricular communication, in effect, is a supracristal ventricular septal defect and is a result of the failure of the distal border of the conal septum to find a truncal septum with which to fuse.

The hypoplastic truncal cushions have failed to partition the truncus arteriosus: Each has simply formed an arterial valve cusp. The position of the two cusps derived from the intercalated valve cushions is abnormal in that they are located anteriorly and posteriorly, rather than left anteriorly and right posteriorly as in a normal embryo of the same age (Fig. 2F). As pointed out previously[20] for the less extreme forms of the anomaly, this is because the hypoplastic conal cushions have not fused, resulting in a "sprung" right ventricular outflow tract and dextroposition of the aorta, caused by the lack of transfer of the posteromedial portion of the conus cordis to the left ventricle. Therefore, there is absence of the normally occurring counterclockwise rotation, as seen from above, of the truncus arteriosus (that is, the combined arterial roots) that should have taken place at this stage of development.

The leftward shift of the right sixth aortic arch has taken place normally, and the aorticopulmonary septum has developed normally (Fig. 2D). This has resulted in a short pulmonary trunk arising from the left side of the common trunk, a condition typical for persistent truncus arteriosus, type 1. As in most cases of persistent truncus arteriosus, the distal portions of both sixth arches have involuted early in development and the ductus arteriosus is therefore absent.

A single coronary artery with the branching pattern and distribution as seen here is not an uncommon associated anomaly. It was present, for example, in 3 of the 49 cases of persistent truncus arteriosus described by Lampertico.[26]

Discussion

Analysis of the embryo described in this paper and the two specimens with persistent truncus arteriosus, type 1 reported by Shaner[22] and by Maron and Hutchins[23] strongly supports the most widely held view that persistent truncus arteriosus is due to failure of septation of the truncus arteriosus, particularly when considered in the light of the observations made on its littermates and on other embryos from the same strain of dogs.[20]

Anatomic type of persistent truncus arteriosus: We agree with Dekker[27] that there is no real justification for the view held by some authors that persistent truncus arteriosus, type 1 represents a partial form of the anomaly and that only the more uncommon forms with pulmonary arteries arising independently from the

trunk (types 2 and 3 of Collett and Edwards) should be considered complete. Furthermore, it is incorrect to refer to Collett and Edwards' type 5 (now considered by most, including Edwards, to be an aorticopulmonary septal defect) as a partial form of persistent truncus arteriosus.[9]

We further agree with Dekker[27] that persistent truncus arteriosus, type 1 (we would add "with an infundibular septum") is really the "pure" form, resulting from the single developmental error of lack of septation of the embryonic truncus arteriosus, and is quite complete. In types 2 and 3 there is an *associated lesion*—absence of the aorticopulmonary septum.[27,28] Strictly speaking, these types should be referred to as "persistence of the truncus arteriosus *and of the aortic sac.*" Absence of the infundibular septum also is an associated lesion. Because of the difficulties in differentiation alluded to earlier, the exclusion of type 4 as a form of persistent truncus arteriosus may well have some merit. Nevertheless, we agree with Humphreys,[8] Dekker[27] and Thiene[28] that theoretically there is no particular reason why type 4 could not occur. It is entirely possible that failure of truncal septation could be associated with absence or very early involution of the sixth pair of aortic arches. In such cases the aorticopulmonary septum obviously would not develop either. However, any apparently genuine case of persistent truncus arteriosus type 4 in which there is a perfectly formed tricuspid arterial valve should be viewed with suspicion. In fact, even if the valve is quadricuspid some doubt remains because an aortic valve, on rare occasions, can be quadricuspid as either an isolated or an associated lesion. Glas,[29] for example, reported a unique case with overriding aorta, infundibular stenosis, small tricuspid pulmonary valve (probably a case of tetralogy of Fallot) and a quadricuspid aortic valve.

Persistent truncus arteriosus—a form of tetralogy of Fallot with pulmonary atresia?: We are uncertain exactly why Van Praagh and Van Praagh[13] reject the concept of truncal septation as the underlying anomaly in persistent truncus arteriosus and instead consider it a "pseudo-truncus," that is, a form of tetralogy of Fallot with subpulmonary infundibular atresia and partial or complete absence of the aorticopulmonary septum. As nearly as we can determine, their line of reasoning is based on some observed anatomic similarities between cases of tetralogy of Fallot and persistent truncus arteriosus. One is that the ventricular septal defect and the anatomy of the outflow tract in the two conditions are similar (but not identical). A second is that the valve in persistent truncus arteriosus is usually tricuspid and therefore considered an aortic valve, the pulmonary valve being absent. In cases with a quadricuspid truncal valve this valve is believed to be the aortic valve plus a remnant of pulmonary valve. The large incidence of right aortic arch and the usual absence of associated anomalies are cited as less direct evidence.

Recently Crupi et al.[30] compared the anatomy of persistent truncus arteriosus with that of 24 specimens of tetralogy of Fallot with pulmonary atresia and concluded that the two conditions are morphologically distinct. Our own observations on 25 and 43 specimens, respectively, of persistent truncus arteriosus and tetralogy with pulmonary atresia are in agreement with their view. In any case, we believe that great caution should be exercised in basing far-reaching conclusions on the pathogenesis of a malformation or group of malformations solely on morphologic similarities between structures present in postnatal hearts.

Morphology of the truncal valve: The observation that the truncal valve, when tricuspid, always has equal-sized cusps and is anatomically indistinguishable from the aortic valve[13] is at variance with the findings of others.[7,26,28,30,31] Among 58 reported cases of persistent truncus arteriosus in which the truncal valve was described or illustrated in detail,[7,26,31] 38 were tricuspid. In 24 of these the cusps were unequal in size or contained a raphe, or both. In only 14 cases was there a "perfect" tricuspid valve. Among 10 cases of our own, 6 had a tricuspid valve, but only 1 was perfect. Only 34 percent of tricuspid valves and 22 percent of all valves in cases of persistent truncus arteriosus were therefore truly tricuspid. The width and length of the cusps were unequal in all of Thiene's cases,[28] the cusps were abnormal in shape and length in all but 2 of the 46 cases with tricuspid valves reported by Crupi et al.[30] In tetralogy of Fallot, on the other hand, pronounced inequality of the aortic valve cusps, a raphe in one of them or an abnormal number of cusps is decidedly rare. Inequality of cusp size or the presence of a raphe in a cusp has long been a recognized indication of dual origin of such a cusp.[7] Most truncal valves, even if they appear to be tricuspid, are actually derived from four or more anlagen.

Van Praagh and Van Praagh's contention,[13] restated by Calder et al.,[16] that cases with two well developed arterial valves and no ventricular septal defect but with a large communication between the ascending aorta and the pulmonary trunk also should be classified as forms of "truncus arteriosus communis" (note the omission of the word "persistent") has been disputed by Goor and Lillehei,[32] Edwards[18] and Crupi et al.[30] We agree with the latter authors that cases with two well developed arterial valves are instances of large aorticopulmonary window (aorticopulmonary septal defect) and should not be considered forms of persistent truncus arteriosus.

Truncus arteriosus communis versus persistent truncus arteriosus (communis): The controversy concerning the definition and pathogenesis of persistent truncus arteriosus has clearly been created by the, in this case, inappropriate use of the term "truncus arteriosus communis" instead of the correct phrase "persistent truncus arteriosus (communis)." This is not merely a matter of semantics; there is a fundamental difference in meaning between the two terms. Van Praagh,[17] in defending his classification of aorticopulmonary window as a form of persistent truncus arteriosus in his reply to Edwards' editorial,[18] argues quite correctly that the Latin phrase "truncus arteriosus communis" simply means common arterial trunk. The

term as employed by Van Praagh appears to be used in the same sense that a common origin from the aortic arch of the right subclavian and both common carotid arteries (an occasional variant in human anatomy) is at times referred to as a "common (brachiocephalic) trunk." Truncus arteriosus therefore is used in an *anatomic* sense for a *postnatal* condition. "Truncus arteriosus" as used in the term "persistent truncus arteriosus," on the other hand, refers to a part of the embryonic heart, specifically the distalmost arterial end of the intrapericardially located bulboventricular loop. Its wall consists of myocardium and its interior is lined with endocardial cushion tissue. It is *not* an artery. In normal development, as stated earlier, it is partitioned by the truncal septum and eventually develops into the aortic and pulmonary roots only, that is, the sinuses of Valsalva and the valve cusps. The ascending aorta and pulmonary trunk are derived from the aortic sac, which *is* an artery, and is partitioned by an invagination of its posterior wall, the aorticopulmonary septum. The term "persistent truncus arteriosus (communis)" indicates that, in essence, the original embryonic condition of a single undivided structure has been retained. Its equivalent in the postnatal heart is the truncal root, that is, the truncal sinuses of Valsalva and valve cusps, *not* the common arterial trunk distal to it. Therefore, the use of the term truncus arteriosus communis for total absence of the aorticopulmonary septum, although technically correct (except that it still does not specify the particular common arterial trunk to which reference is made), cannot be recommended because it undoubtedly would cause confusion and has already done so.

Addendum

Since the manuscript went to press we encountered a second case of persistent truncus arteriosus, type 1 in a pup of the same strain of Keeshond. There was a quadricuspid moderately dysplastic truncal valve overriding a supracristal ventricular septal defect. The proximal part of the crista supraventricularis was present but it had a very wide fibrous raphe (conal septal fusion line). The medial papillary muscle was absent. The ventricular septal defect was bordered by nodular fibrous tissue. A second smaller ventricular septal defect was present in the muscular part of the ventricular septum anterior to the trabecula septomarginalis. The aortic arch was on the left side and there was a small persistent left superior vena cava.

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Electrophysiologic Effects of Hydralazine on Sinoatrial Function In Patients With Sick Sinus Node Syndrome

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The electrophysiologic effects of hydralazine were evaluated in nine hypertensive patients with sinoatrial dysfunction. Intravenous hydralazine, 0.15 mg/kg, caused no significant reduction in arterial blood pressure. Yet this dose of hydralazine increased heart rate from 61.9 ± 4.1 beats/min (mean ± standard error of the mean) to 68.6 ± 4.9 ($P < 0.001$). Sinus nodal recovery time upon termination of atrial pacing shortened from 3,207 ± 1,098 to 2,064 ± 573 msec ($P < 0.05$) and second escape cycles shortened as well ($P < 0.025$). Acceleration of heart rate and abbreviation of recovery time did not closely correlate with change in blood pressure ($r = 0.41$ and 0.18, respectively). Junctional escape beats became more frequent and junctional escape time shortened from 2,525 ± 692 to 1,705 ± 382 msec ($P < 0.05$). Sinoatrial conduction time tended to shorten, but a significant change was not observed. Atrial tachyarrhythmias did not occur and atrial refractoriness was unchanged. Thus, a minimal blood pressure response to hydralazine was associated with enhanced automaticity. Hydralazine merits clinical trial for treatment of sick sinus syndrome with concomitant hypertension.

Despite the comparatively benign prognosis associated with asystole originating from sinoatrial dysfunction, symptoms of sick sinus syndrome respond poorly to current pharmacologic approaches and permanent pacing is usually required.[1–9] Thus, there is need for a long-acting oral preparation that will alleviate symptoms in patients with milder forms of sick sinus syndrome and obviate the need for pacemaker insertion.

Moreover, many patients with sick sinus syndrome are of advanced age and require antihypertensive therapy.[5–9] Hydralazine is a long-acting antihypertensive agent[10] with prominent cardioaccelerator effects.[11–14] The tachycardia induced by hydralazine may be partly central in origin as well as a reflex response to decreased blood pressure.[15–18] Certainly, hydralazine does not cause the reduction in sympathetic response common to most antihypertensive agents.[19] Thus, the cardioaccelerating action of hydralazine might ameliorate symptomatic bradycardia and asystole without attendant side effects of vagal blockade.

The purpose of this investigation is to (1) establish the electrophysiologic efficacy of hydralazine on sinoatrial function; (2) evaluate the efficacy of hydralazine in restoring measurements indicative of sinoatrial dysfunction toward normal; and (3) correlate the antihypertensive effect of hydralazine with changes in automaticity.

Methods

Patients: The electrophysiologic effects of intravenous hydralazine were studied in nine hypertensive patients in the postabsorptive state after they had given informed written consent. They were evaluated for sinoatrial dysfunction because of syncope or dizziness unexplained by neurologic evaluation, labyrinthine dysfunction, carotid sinus hypersensitivity, orthostatic hypotension or

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TABLE I

Clinical Features of Patients With Sick Sinus Syndrome Receiving Hydralazine

Case no.	Age (yr) & Sex	Arrhythmias	Symptoms	Medications
1	74 M	SB, sinus arrest, S-A block (Mobitz I)	Syncope	None
2	76 F	SB, sinus arrest	Syncope	None
3	72 F	SB, sinus arrest or S-A block (Mobitz I)	Dizzy spells	None
4	78 F	SB, S-A block (Mobitz II)	Syncope	Digoxin
5	90 F	SB, S-A block (Mobitz II)	Dizzy spells, cerebral embolus	None
6	67 M	SB	Syncope	None
7	52 F	SB	Syncope	Furosemide
8	61 F	SB	Syncope	Thiazide
9	69 M	SB	Syncope	None

S-A = sinoatrial exit block; SB = sinus bradycardia.

drug history. All had sinus bradycardia recorded on at least two occasions and five had additional rhythm disturbances characteristic of sick sinus syndrome (Table I). Patients 1, 3 and 4 were clearly symptomatic because of arrhythmia; the others were referred to establish a diagnosis of sinoatrial dysfunction. No patient had clinical evidence of congestive heart failure at the time of study. None had received antihypertensive or cardioactive therapy within 72 hours of study, except as indicated in Table I.

Procedures for electrophysiologic study: A quadripolar catheter inserted by way of the right basilic vein was used for atrial stimulation and for recording an electrogram from the vicinity of the superior vena cava/right atrial junction. The right brachial artery was catheterized and pressure was monitored using a Statham P23-db transducer. When clinically indicated, His bundle electrograms were recorded from a tripolar catheter inserted by way of the right femoral vein. Recordings were made at 100 mm/sec paper speed with an Electronics for Medicine DR-12 multichannel oscilloscope. Intracavitary leads were recorded at 40 to 500 hertz and surface leads I, II, aVF and V_1 were simultaneously recorded.

Atrial pacing was performed with twice threshold stimuli provided by a Grass S88 stimulator with SIU5 isolation units. Coupling intervals for atrial extrastimulation were determined with a Quartec APS-3C controller. Cycle length (average of 10 beats) and responses to atrial extrastimulation and overdrive pacing were determined before and 30 minutes after intravenous infusion of 0.15 mg/kg of hydralazine *infused intravenously* over a period of 5 minutes. This dose of hydralazine was chosen to minimize hypotensive effects. The maximal antihypertensive effect of hydralazine is seen within 30 minutes of intravenous infusion.[11]

Escape intervals were determined after abrupt termination of 30 to 60 seconds of overdrive atrial pacing. Pacing was first performed at a rate just sufficiently rapid to capture the atrium. Subsequent pacing rates were increased by increments of 10 beats/min to a rate of 150 beats/min. At least 30 seconds was allowed between determinations. In our laboratory this sequence and duration of atrial pacing have yielded maximal escape intervals less than 1,400 msec (mean + 2 standard deviations) in three separate series of normal subjects.[20–22]

TABLE II

Heart Rates and Escape Intervals After Atrial Pacing

Case no.	State	Heart Rate (beats/min)	Sinus Nodal Recovery Time (max) (msec)	Second Escape Interval (max) (msec)	Junctional Recovery Time (max) (msec)
1	Basal	86	1,480	1,685	. . .
	Hydralazine	103	1,030	630	. . .
2	Basal	71	7,300	5,365	3,430
	Hydralazine	77	2,900	3,000	2,140
3	Basal	72	1,470	1,560	1,460
	Hydralazine	73	1,200	920	950
4	Basal	59	1,570	1,300	1,230
	Hydralazine	63	1,350	1,160	1,180
5	Basal	50	10,400	*	3,980
	Hydralazine	55	6,400	*	2,550
6	Basal	49	1,750	1,700	. . .
	Hydralazine	56	1,660	1,600	. . .
7	Basal	56	1,750	1,780	. . .
	Hydralazine	63	1,590	1,350	. . .
8	Basal	61	1,610	1,570	. . .
	Hydralazine	64	1,130	1,060	. . .
9	Basal	53	1,540	1,300	. . .
	Hydralazine	63	1,320	1,180	. . .
Mean	Basal	61.9	3,207	2,033	2,525
± SEM		4.1	1,098	477	692
Mean	Hydralazine	68.6	2,064	1,363	1,705
± SEM		4.9	573	253	382
Δ		6.7	1,143	670	820
± SEM		1.6	580	266	327
P		<0.001	<0.05	<0.025	<0.05

* Not determined because junctional rhythm followed each first sinus escape.
Δ = change; max = maximal; *P* = probability; SEM = standard error of the mean.

Additionally, escape intervals were determined after 1,3 and 5 minutes of atrial pacing at 120 beats/min.

Definitions: *Sinus nodal recovery time* was taken as the longest interval from the last paced atrial electrogram to the first spontaneous atrial electrogram after termination of any rate of pacing. Only escape intervals terminated by P waves of apparent sinus origin were considered. The longest second escape interval after termination of pacing was also determined (the P-P interval following the sinus nodal recovery time if terminated by a P wave of apparent sinus origin). Second escape intervals are often the prominent abnormality in patients with sinoatrial dysfunction, particularly in patients with sinoatrial exit block.[23] Corrected recovery times were calculated by subtraction of or division by the basic prepaced cycle length.

After termination of pacing, some patients had predominantly junctional escape beats that were typical of sick sinus syndrome. An early junctional escape beat, induced by a therapeutic agent that accelerates automaticity, is just as significant in alleviation of symptoms as an early sinus recovery beat.[20] Therefore, *junctional recovery time,* the longest junctional escape interval, was determined if junctional escape beats were present both before and after infusion of hydralazine.

Sinoatrial conduction times were determined from the pause after atrial extra beats applied in sinus rhythm, as previously described.[22] Sinoatrial conduction time was calculated by subtraction of the preceding basic cycle length from the pause after an extra beat, utilizing at least 10 coupling intervals within the last half of atrial diastole that were sufficiently early to be followed by a relatively constant pause (the plateau phase).[24] Sinoatrial conduction time determined after administration of hydralazine required correction for the curtailed basic cycle length. This correction was roughly approximated by utilizing data obtained by Reiffel et al.[25] from patients with sinus arrhythmias, as follows: Corrected conduction time = sinoatrial conduction time minus 0.31 (prehydralazine cycle length minus posthydralazine cycle length).

The atrial effective refractory period was considered the longest atrial to extrastimulus coupling interval not resulting in an atrial premature depolarization.

Statistical comparisons were made with a paired *t* test. Electrophysiologic changes after administration of hydralazine were compared with blood pressure changes using a product moment correlation.

After cardiac catheterization, and for at least 24 hours, patients receiving hydralazine were closely monitored for arrhythmias in the cardiac care unit.

Results

All patients had evidence of sinoatrial dysfunction on basal electrophysiologic testing (Tables II and III). All had sinus nodal recovery times of more than 1,400 msec, and in all but two patients sinus nodal recovery time minus cycle length was more than 550 msec. In six patients, sinus nodal recovery time/cycle length ratio was more than 1.63 and in five the second escape cycle/cycle length ratio was more than 1.60.[23] Sinoatrial conduction times of more than 230 msec were recorded in five patients, including three with conduction times of more than 310 msec.[22,26]

TABLE III

Results of Atrial Extrastimulation

Case no.	State	Sinoatrial Conduction Time (msec)	Corrected Conduction Time (msec)*	Atrial Effective Refractory Period (msec)
1	Basal	343		270
	Hydralazine	342	305	270
2	Basal	248		300
	Hydralazine	245	205	300
3	Basal	364		330
	Hydralazine	388	383	300
4	Basal	314		310
	Hydralazine	257	235	310
5	Basal	†		430
	Hydralazine	380	349	430
6	Basal	63		300
	Hydralazine	156	106	320
7	Basal	236		240
	Hydralazine	215	184	230
8	Basal	184		340
	Hydralazine	88	75	320
9	Basal	188		310
	Hydralazine	208	153	340
Mean	Basal	243‡		314
± SEM		35		18
Mean	Hydralazine	237‡	206‡	313
± SEM		34	36	18

* Corrected conduction time = sinoatrial conduction time minus 0.31 (prehydralazine cycle length minus posthydralazine cycle length).
† Sinoatrial conduction time could not be determined because of advanced sinoatrial entrance block.
‡ Case 5 not included.
SEM = standard error of the mean.

TABLE IV

Effects of Hydralazine on Blood Pressure

Case no.	Basal Pressure (mm Hg) S/D	Mean	Posthydralazine Pressure (mm Hg) S/D	Mean
1	230/118	160	210/92	130
2	210/80	125	180/60	100
3	165/60	92	180/52	90
4	200/75	90	210/72	92
5	170/60	85	170/80	94
6	160/80	108	140/70	95
7	190/72	130	228/100	140
8	210/95	125	215/90	120
9	190/98	136	176/92	118
Mean	192/82	117	190/79	109
± SEM	7.8/6.2	8.3	9.3/5.4	6.2

Blood pressure response to hydralazine (Table IV, Fig. 1): All patients had at least systolic hypertension. There was no significant decrease in blood pressure after infusion of 0.15 mg/kg of hydralazine. Average systolic pressure decreased from 192 ± 8 mean ± standard error of the mean to 190 ± 9 mm Hg (difference not significant), mean pressure decreased from 117 ± 8 to 109 ± 6 mm Hg (difference not significant) and diastolic pressure from 82 ± 6 to 79 ± 5 (also not significant). Five patients had no decrease in systolic blood pressure and three had no decrease in mean blood pressure.

Patient 5 had symptomatic hypotension (blood pressure as low as 90/70 mm Hg) intermittently when paroxysms of junctional rhythm appeared for the first time after hydralazine, resulting in loss of atrial transport function. In only one other patient (Case 6) was a normal blood pressure attained during the study period. Other untoward effects of hydralazine were not seen.

Heart rate and escape cycle responses (Table II): Heart rate was increased after hydralazine in all patients (Fig. 1), from a mean of 61.9 ± 4.1 to 68.6 ± 4.9 beats/min ($P < 0.001$). The increased heart rate did not correlate closely with the reduction in systolic pressure ($r = 0.45$) or mean pressure ($r = 0.41$). Heart rate increased in all five patients whose systolic pressure did not decrease. Patients 4, 5 and 7 had an increase in mean pressure but heart rate increased by 4 to 7 beats/min. Thus, the average reductions in systolic pressure (1 percent) and in mean pressure (7 percent) were associated with a somewhat greater increase in heart rate (11 percent).

Sinus nodal recovery time was abbreviated after hydralazine in all patients (Fig. 1), changing from 3,207 ± 1,098 to 2,064 ± 573 msec ($P < 0.05$). Recovery time became less than 1,400 msec in five patients. The decrease in recovery time did not correlate with the change in systolic or mean arterial pressure ($r = 0.31, 0.18$). In the five patients without reduced systolic pressure, sinus nodal recovery time was shortened by an average of 1,026 msec. The patients with an increase in mean pressure had shortening of recovery time by 220, 4,000 and 160 msec, respectively. Thus, the group reductions of 1 percent in systolic arterial pressure and 7 percent in mean pressure were associated with a 36 percent shortening of sinus nodal recovery time. The normal response of postpacing escape intervals to change in blood pressure is not known. However, Figure 2 illustrates that the percent shortening in sinus nodal recovery time was disproportionate, although not neces-

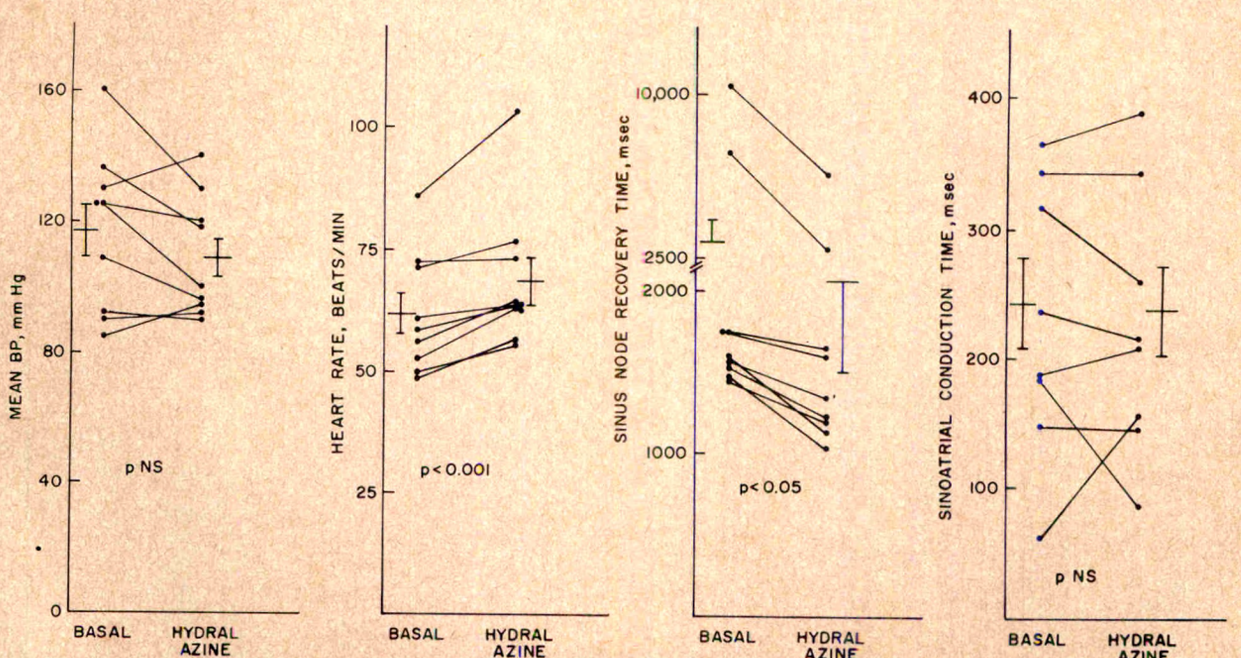


FIGURE 1. Mean arterial blood pressure (BP), heart rate, sinus nodal recovery time and sinoatrial conduction time before and 30 minutes after infusion of 0.15 mg/kg of hydralazine in nine subjects. The **horizontal lines** indicate mean ± standard error of the mean. An insignificant change in blood pressure was associated with consistent acceleration of heart rate and shortening of sinus nodal recovery time. NS = not significant; p = probability.

sarily abnormally so, to the percent reduction in blood pressure. This was true for the majority of patients, the data falling below the line of identity even when recovery time was corrected for the increased heart rate. Second escape intervals were also abbreviated in all patients, from 2,033 ± 477 to 1,363 ± 253 msec (P <0.025).

When corrected for the accelerated heart rate, the abbreviation of sinus nodal recovery time after hydralazine was inconsistent because the effect on heart rate was greater than the effect on escape cycles in some patients. Nonetheless, sinus nodal recovery time minus cycle length became less than 550 msec in five patients, and was abbreviated in eight of nine patients, from 2,194 ± 1,089 to 1,159 ± 552 msec (P <0.06.) The sinus nodal recovery time cycle length ratio became less than 1.63 in five patients, was reduced in six of nine patients and changed from 3.17 ± 1.04 to 2.22 ± 0.51 (P <0.07). The second escape cycle/cycle length ratio was reduced in six of eight patients, from 2.18 ± 0.60 to 1.57 ± 0.33 (P <0.05) and was less than 1.60 in all but one patient after hydralazine.

Four patients had junctional escape beats before as well as after hydralazine, and junctional recovery time was abbreviated in all, from 2,525 ± 692 to 1,705 ± 382 msec. The change in junctional recovery time was significant (P <0.05) despite the small number of patients. Only one patient had a change in junctional recovery time greater than a change in sinus nodal recovery time, but junctional escapes and junctional rhythm were more evident in all patients after hydralazine.

Response of sinoatrial conduction to hydralazine (Table III): Hydralazine shortened sinoatrial conduction time in five of eight patients, including the three patients with an initial conduction time greater than 310 msec (Fig. 1). In an additional patient (Case 5), sinoatrial conduction time could not be determined because of advanced sinoatrial entrance block. Entrance block was eliminated by hydralazine in this patient.

The average abbreviation of sinoatrial conduction time was small (−5.1 msec ± 20) (not significant). However, sinoatrial conduction is delayed by increasing heart rate, much as the A-H interval prolongs as a function of atrial pacing rate.[25] When sinoatrial conduction times were crudely corrected for the more rapid heart rates invariably seen after hydralazine, the more pronounced reduction (−36.3 msec ± 17.0) did achieve statistical significance (P <0.05).

Atrial response to hydralazine (Table III): The atrial effective refractory period was shortened in only three patients despite the increased heart rate after hydralazine, and the group change in refractory period was only −1 msec. Perhaps as a consequence, atrial tachycardias and atrial vulnerability to extrastimulation were not encountered in the laboratory after hydralazine. No tachyarrhythmias were identified during monitored periods after catheterization.

Discussion

Pharmacologic therapy is generally insufficient for sick sinus syndrome,[1–9] in part because of intolerable side effects or lack of sustained drug action. It is unfortunate that pacemaker therapy is usually requisite because many patients with sick sinus syndrome have relatively mild symptoms with a risk for sudden death that is not as grave as in patients with a potential for complete A-V block.[1–9]

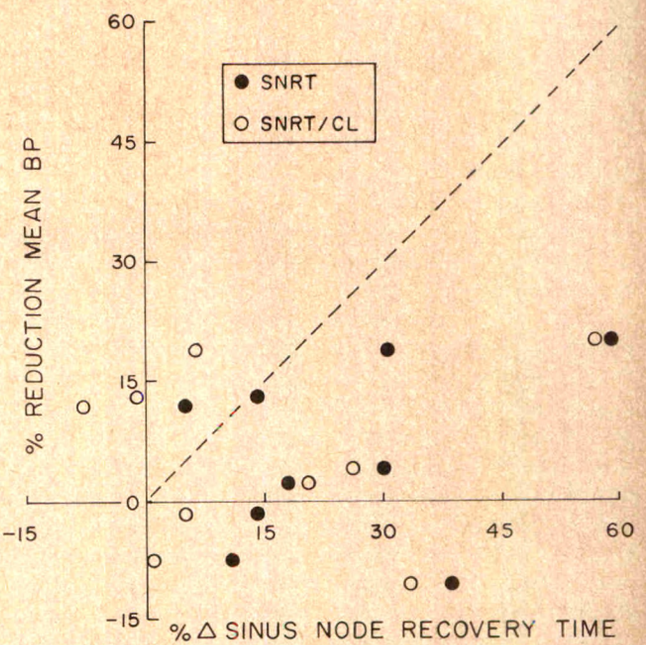


FIGURE 2. Percent reduction in mean arterial blood pressure (BP) after hydralazine, 0.15 mg/kg intravenously, compared with percent reduction in sinus nodal recovery time (SNRT) **(solid circles).** Data from most subjects fall below the line of identity, even when corrected for the decreased cycle length seen after hydralazine (sinus nodal recovery time divided by cycle length [SNRT/CL]) **(open circles).** The disproportionate reduction in sinus nodal recovery time could reflect an independent cardioaccelerator effect of hydralazine; however, the effect of blood pressure changes on sinus nodal recovery time have never been defined.

Hydralazine as a potential drug for therapy of sick sinus syndrome was investigated for the following reasons: (1) It causes such prominent cardiac acceleration that it has been relatively contraindicated in coronary heart disease[13]; (2) it is often an appropriate therapeutic agent in patients with sick sinus syndrome, for example, because many of these patients are old and require concomitant control of hypertension. The vasodilator action of the drug apparently is direct, on the vessel wall itself, and autonomic responses, often blunted in sick sinus syndrome, are not aborted by hydralazine; and (3) taken orally, the drug has a long duration of action and perhaps is effective when taken twice daily.[10]

Mechanisms of cardioaccelerator action: It is noteworthy that enhancement of automaticity seen in our patients with sick sinus syndrome, as reflected by faster heart rates and shorter escape cycles, was associated with minimal and inconsistent reduction in blood pressure. Perhaps more striking changes in automaticity would have occurred with more hypotensive doses of hydralazine. Nonetheless, hydralazine appeared to cause changes in automaticity that could not be ex-

plained by a reflex response to decreased blood pressure. Central or direct cardioaccelerator effects of hydralazine have been suggested because (1) increased heart rate usually precedes decreased blood pressure after intravenous infusion[15,27,28]; (2) tachycardia often outlasts hypotension[29]; (3) tachycardia can be elicited by selective brain infusion[16]; and (4) increases in heart rate exceed those seen when equivalent blood pressure reduction is caused by other vasodilators such as sodium nitroprusside.[28,30]

Reduction of peripheral vascular resistance may be associated with unchanged blood pressure if cardiac output is proportionally increased. In patients with elevated left ventricular filling pressures, cardiac output is increased by hydralazine without a major increase in heart rate,[30,31] presumably because reduction in outflow impedance increases stroke volume. In our patients with sick sinus syndrome, left ventricular filling pressures were probably normal and cardiac output may have been reflexly increased by a faster heart rate, in that manner maintaining blood pressure. However, Franciosa et al.[30] considered the possibility of a direct cardiac stimulating effect of hydralazine even in heart failure because heart rate tended to increase after hydralazine but was unchanged during nitroprusside infusion, even though blood pressure was lower and venous capacitance greater with nitroprusside.

Clinical implications: Our results suggest a beneficial effect of hydralazine on the bradycardia and asystole of sick sinus syndrome. Hydralazine accelerated heart rate; by enhancing both junctional and sinus automaticity, it diminished the pauses after atrial overdrive pacing that are presumed to be analogous to the symptomatic pauses of tachycardia-bradycardia sequences. Parenthetically, the actual pause probably reflects symptomatic asystole more directly when it is not corrected for cycle length; it is the duration of the pause that causes symptoms. Also, sinoatrial conduction may have improved as well after hydralazine. Thus, our data suggest that hydralazine is useful in treatment of hypertension in the patient with sick sinus syndrome.

Hydralazine might be efficacious in patients with sick sinus syndrome with normal blood pressures. In our study, cycle length and escape cycles were abbreviated with only modest reductions in arterial pressure. Sustained therapy without concomitant diuresis might cause even less reduction in blood pressure but the cardioaccelerator action of hydralazine, if central or direct, might persist. However, we do not now recommend hydralazine for normotensive patients with sick sinus syndrome because such patients have not been evaluated.

Long-term clinical experience in hypertensive patients is requisite before the results of our laboratory study can be translated into recommended therapy because (1) a *sustained* cardioaccelerator effect of hydralazine in sick sinus syndrome remains to be established; (2) improvement in heart rate, escape cycles and sinoatrial conduction time cannot be directly translated into symptomatic improvement; and (3) accentuation of tachyarrhythmias by hydralazine is possible, even though we observed no tachyarrhythmias and believe that amelioration of bradycardia and asystole should reduce the frequency of tachycardias.[32] We therefore recommended permanent pacemaker therapy for many of our patients.

The results of our study suggest that hydralazine is effective in improving various electrophysiologic indicators of sick sinus syndrome as measured in the catheterization laboratory. Long-term clinical trial in selected patients with sick sinus syndrome with hypertension appears to be indicated.

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Single and Multiple Dose Pharmacokinetics of Oral Quinidine Sulfate and Gluconate

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The pharmacokinetics of oral quinidine sulfate and quinidine gluconate were compared in seven healthy volunteers in a two part pharmacokinetic study. Part I was a single dose crossover trial assessing absorption and elimination of quinidine sulfate (400 mg, equivalent to 331 mg of quinidine base) and quinidine gluconate (495 mg, equivalent to 309 mg of quinidine base). Mean kinetic values for the sulfate and gluconate preparations, respectively, were: peak serum quinidine level 2.07 versus 1.24 μg/ml ($P < 0.025$); time of peak concentration 1.61 versus 3.64 hours after the dose ($P < 0.02$); first order absorption half-life 41.1 versus 61.2 minutes ($P < 00.1$); elimination half-life 6.1 versus 6.3 hours (difference not significant); absolute systemic availability (based upon comparison with intravenous data from the same subjects) 86.0 versus 76.5 percent (difference not significant) using area under the serum concentration curve, or 83.7 versus 73.6 percent ($P < 0.05$) using cumulative 48 hour urinary excretion of quinidine. The findings indicate that absorption of quinidine gluconate is slightly less complete but much less rapid than that of quinidine sulfate.

Part II evaluated steady state kinetics of both preparations in a crossover trial in the same subjects. Maintenance dosing schedules were 200 mg of quinidine sulfate every 6 hours versus 495 mg of quinidine gluconate every 12 hours. Systemic availability of the gluconate at the steady state level was 10 percent less (based upon area under the serum concentration curve) or 7 percent less (based upon urinary excretion of quinidine) than that of the sulfate, but the differences were not significant. Interdose fluctuation in serum quinidine concentrations during the gluconate trial averaged 70 percent, which was not significantly different from the average of 67 percent during the sulfate trial. However, variation within and between subjects in minimal steady state levels with quinidine gluconate (15.6 and 16.0 percent, respectively) was greater than with quinidine sulfate (7.2 and 9.9 percent, respectively). Steady state concentrations during the multiple dose trial were not accurately predicted from single dose pharmacokinetics, either for quinidine sulfate ($r = 0.45$) or quinidine gluconate ($r = -0.12$), but deviation of observed from predicted concentrations tended to be greater with quinidine gluconate. The slow absorption of quinidine from the gluconate preparation allows maintenance therapy on a 12 hourly dosage schedule with acceptable interdose fluctuation in serum levels. Variability within and between subjects in absorption kinetics tends to be greater with quinidine gluconate than with the more rapidly absorbed sulfate salt.

Patient compliance is an important consideration during long-term antiarrhythmic therapy of ambulatory patients. Clinicians must choose not only the correct antiarrhythmic agent but also the dosage form and dosing schedule that are likely to maximize compliance. The need for multiple daily doses is an important drawback to the use of the quinidine

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TABLE I

Subject Characteristics

Case no.	Age (yr) & Sex	Weight (kg)	Creatinine Clearance (ml/min)
1	29F	68.2	91
2	31M	79.5	144
3	27F	61.4	72
6	30M	69.5	106
7	25M	72.3	119
8	31M	70.0	126
10	29F	57.7	92
Mean	28.9	68.4	107.1
±SE	±0.8	±2.7	±9.2

sulfate, the traditional oral quinidine preparation. Recent studies suggest that quinidine gluconate, promoted as a "slow-release" oral quinidine dosage form, is more slowly absorbed than quinidine sulfate[1] and thus may be suitable for less frequent and more convenient dosing. The present study assessed the comparative pharmacokinetics of oral quinidine sulfate and gluconate in healthy volunteers after single and multiple doses.

Methods

Seven healthy male and female volunteers (Table I) participated in a two part pharmacokinetic study. Part I was a single dose crossover comparison of intravenous quinidine lactate, oral quinidine sulfate and oral quinidine gluconate.[1] Part II compared the two oral preparations in the same subjects during simulated long-term therapy.

Procedure: *Part I:* For the intravenous quinidine trial, 275 to 300 mg of quinidine base as the lactate salt was given intravenously with a constant rate infusion pump over 15 minutes.[1] For the oral quinidine trials, subjects ingested 400 mg of quinidine sulfate (Parke-Davis Laboratories) (two 200 mg tablets) or 495 mg of quinidine gluconate (Cooper Laboratories (one and a half 330 mg tablets) with 100 ml of water in the fasting state. At least 1 week elapsed between the three trials, and the order of exposure was random. Venous blood samples were drawn at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3, 4, 6, 8, 12, 18, 24 and 30 hours after the start of the intravenous infusion or after each oral dose. All urine was collected during 48 hours after each dose in the following intervals: 0 to 1, 1 to 2, 2 to 4, 4 to 8, 8 to 24 and 24 to 30 hours. Serum and urine samples were stored at −20° C until the time of analysis.

Part II: The same seven subjects participated in a crossover study of simulated long-term therapy with the two oral quinidine preparations. Quinidine sulfate was given as a loading dose (400 mg) in the fasting state on the morning of the first day. Maintenance doses of 200 mg each were administered at 6, 12, 18 and 24 hours after the loading dose. Venous blood samples were drawn at 0.5, 1.0, 1.5, 2.0, 2.5, 3, 4 and 6 hours after the first, second and last doses. Additional samples were drawn at 8, 12, 18, 24, 30, 36 and 48 hours after the final dose. For the quinidine gluconate trial, a loading dose of 660 mg (two tablets) was given on the morning of the first day, and followed by subsequent maintenance doses of 495 mg (1.5 tablets) at 12 and 24 hours after the initial loading dose. Venous blood samples were drawn at 0.5, 1.0, 1.5, 2.0, 2.5, 3, 4, 6, 8 and 12 hours after the first and last doses; additional samples were taken 18, 24, 30, 36 and 48 hours after the last dose. All urine was collected for 96 hours after the start of both trials in intervals as follows: 0 to 24, 24 to 48, 48 to 72 and 72 to 96 hours. All serum and urine was stored at −20° C until the time of assay.

In one subject (Case 6), several additional samples were drawn. During the quinidine sulfate trial, samples were taken at 0.5, 1.0, 1.5, 2, 3, 4 and 6 hours after the second, third and fourth quinidine dose. During the gluconate trial, samples were taken at the same intervals after the first two doses. An additional trial was performed in one subject (Case 8). This man ingested a 600 mg loading dose of quinidine sulfate, followed by two maintenance doses of 300 mg taken at 12 and 24 hours after the initial dose. The sampling schedule was the same as in the quinidine gluconate trial in Subject 6.

At least 10 days elapsed between the termination of one trial and the start of the next. The order of exposure to the two treatment conditions was random. The total dose of quinidine base administered during the quinidine sulfate trial was 994 mg compared with 1,027 mg during the quinidine gluconate trial.

Analysis of serum and urine: Quinidine concentrations in all serum and urine samples were determined by a modification[1] of the double extraction spectrophotofluorometric technique.[2] The method has a sensitivity limit of approximately 0.02 to 0.03 μg/ml and a coefficient of variation for identical samples of less than 3 percent. Quinidine and its cardioactive reduction product dihydroquinidine are quantitated by this analytic technique, whereas water-soluble polar metabolites are largely excluded. Serum quinidine concentrations determined by this extraction-fluorescence method are very close to or identical with concentrations measured in the same samples using specific chromatographic techniques.[3–6]

Analysis of data: *After single oral doses of the two quinidine preparations,* serum concentrations were analyzed by computer using iterative weighted nonlinear least squares regression analysis.[1,7,8] Data points were fitted to one of the following two functions:

$$C = A(e^{-\beta t} - e^{-k_a t}) \quad (1)$$

$$C = -(A + B)e^{-k_a t} + Ae^{-\alpha t} + Be^{-\beta t} \quad (2)$$

In both of these equations, C is the serum quinidine concentration at time t after the dose, A and B are "hybrid" intercept terms and k_a is the apparent first order absorption rate constant; α and β are "hybrid" exponents representing apparent rate constants for drug distribution and elimination, respectively. In some cases it was necessary to modify the equations by introducing a lag time before the start of absorption. For each set of data the choice between Equations 1 and 2 as functions of "best fit" was made by comparison of the sum of squares of weighted residual errors and by the "scatter" of data points about the function. The hybrid exponents from the fitted function were used to calculate the apparent first order half-life values for drug absorption and elimination.[1,9–11]

Absolute systemic availability (or apparent completeness of drug absorption) for each oral quinidine preparation in each subject was estimated by comparing the dose-corrected area under the 30 hour serum concentration curve (AUC-30) and the dose-corrected 48 hour urinary excretion value (UE-48) for the two oral preparations with that observed in the same subject after intravenous administration of quinidine.

During the multiple dose trial, attention was focused upon the final "steady state" dosage interval, that is, 0 to 6 hours and 0 to 12 hours after the last dose of quinidine sulfate and gluconate, respectively. The following factors were analyzed: the two "minimal" steady state concentrations, drawn just before the last dose and 6 hours after the last dose of quinidine

TABLE II

Single Dose Pharmacokinetics of Oral Quinidine Sulfate and Gluconate

	Quinidine Sulfate*	Quinidine Gluconate*	Value of Student's Paired *t* and Level of Significance (two-tailed test)
Number of subjects in which lag time was observed	3	3	. . .
Peak serum concentration (μg/ml)	2.07 ± 0.24	1.24 ± 0.16	3.07 ($P < 0.025$)
Time of peak concentration (hours after dose)	1.61 (±0.34)	3.64 (±0.82)	3.40 ($P < 0.02$)
First order absorption half-life (min)	41.1 (±5.5)	61.2 (±9.5)	1.91† ($0.05 < P < 0.01$)
First order elimination half-life (hr)	6.09 (±0.48)	6.29 (±0.72)	0.23 (NS)
AUC-30 (percent of intravenous value)	86.0 (±5.6)	76.5 (±6.3)	0.99 (NS)
UE-48 (percent of intravenous value)	83.7 (±4.6)	73.6 (±2.6)	2.87 ($P < 0.05$)

* Values expressed as mean ± standard error.
† Independent *t* value given, because absorption half-life could not be calculated for one subject after quinidine gluconate.
AUC-30 = dose-corrected area under the 30 hour serum concentration curve; NS = not significant; *P* = probability; UE-48 = dose-corrected 48 hour urinary excretion value.

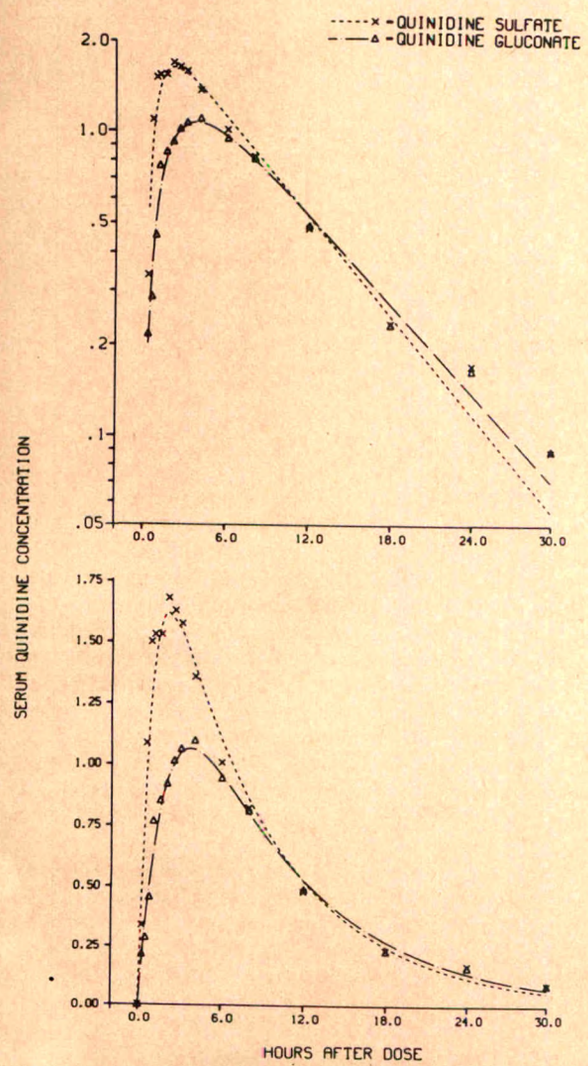


FIGURE 1. Serum quinidine concentrations (μg/ml) after a single oral dose of quinidine sulfate or quinidine gluconate, plotted on semilogarithmic (**above**) and linear (**below**) scales. Each point is the mean serum concentration for all seven subjects at corresponding times. Also shown are the functions of best fit determined from nonlinear least squares analysis.

sulfate (or 12 hours after the last dose of quinidine gluconate); the mean and coefficient of variation (CV = the standard deviation divided by the mean, expressed in percent) of the two minima; the pooled within-subject values of CV, giving an overall estimate of within-subject variability in minimal steady-state levels[12]; the between-subject mean and coefficient of variation determined from the individual mean values, giving an estimate of between-subject variation in the minimal steady state level; the maximal steady state concentration and the percent increase over the minimal level; and the steady state bioavailability, calculated as the area under the serum concentration curve during the final dosage interval corrected for the administered dose of quinidine base.

For each subject the computer-generated functions of best fit after single doses were used to predict the serum concentration curve during the multiple dose schedule.[10,11,13] Differences between observed and predicted minimal steady-state concentrations were analyzed using linear regression.

Results

First Study

Rates of absorption and elimination: Table II summarizes results of the single dose pharmacokinetic study of the two oral preparations (detailed analysis of intravenous quinidine pharmacokinetics is available elsewhere[1]). Peak serum levels after quinidine gluconate were significantly lower and were reached significantly later after the dose than after administration of quinidine sulfate. The difference in peak serum concentrations remained significant even after correction for the difference between the two preparations in dosage of quinidine base. The apparent first order absorption half-life for quinidine gluconate (61.2 minutes) was longer ($0.05 < P < 0.1$) than for quinidine sulfate (41.1 minutes). The mean apparent elimination half-life of quinidine was nearly identical after both dosage forms (6.1 versus 6.3 hours, respectively). The findings indicate the quinidine absorption from the gluconate preparation proceeds at a slower rate than from the sulfate salt, leading to lower peak serum levels achieved later after the dose. However, elimination of quinidine in the postabsorptive phase, is the same with both preparations. Figure 1 shows semilogarithmic and linear plots of the single dose serum concentrations based on mean values from all seven subjects.

Systemic availability: The apparent systemic availability of the sulfate and gluconate salts, based on the dose-corrected

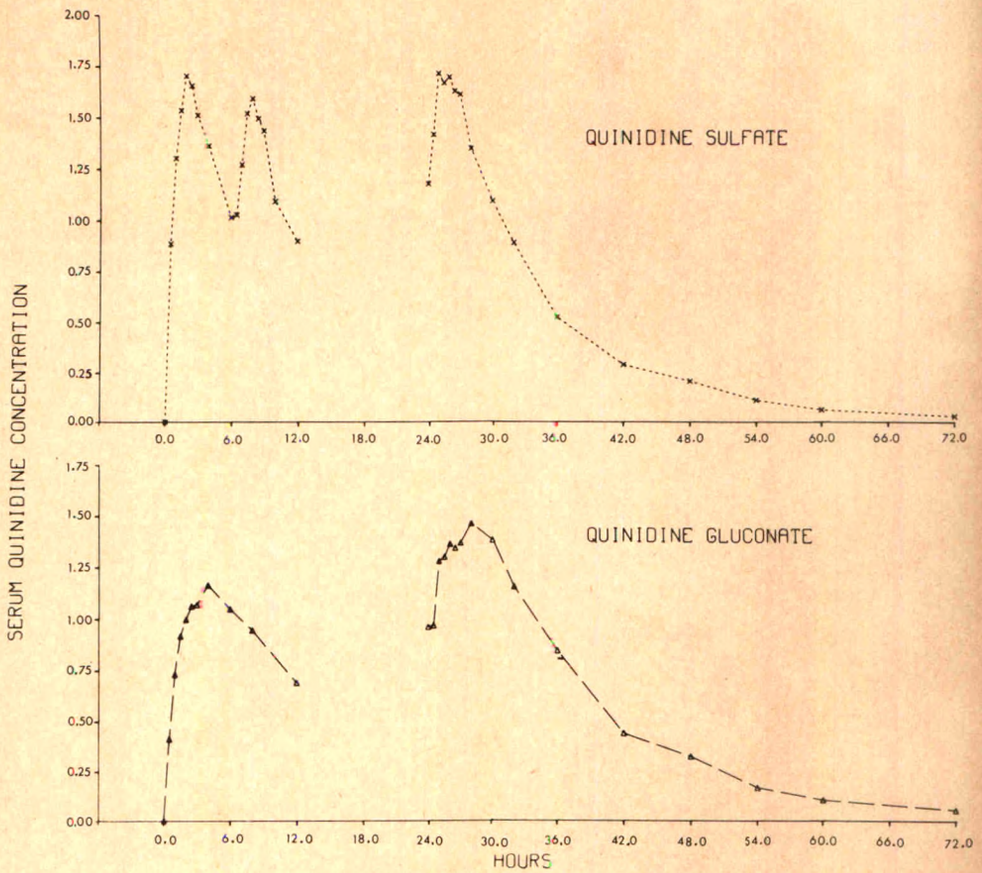


FIGURE 2. Serum quinidine concentrations (μg/ml) during the multiple dose trial with quinidine sulfate (**above**) and quinidine gluconate (**below**). Each point is the mean concentration for all subjects at corresponding times.

TABLE III

Steady State Pharmacokinetics of Quinidine

Case no.	Minimal Steady State Concentration (μg/ml)				Maximal Steady State Concentration (μg/ml)	Percent Increase
	t = 24 hr	t = 30 hr	Mean	CV		
			Quinidine Sulfate			
1	1.137	0.933	1.035	13.9%	1.72	66.18
2	1.021	1.044	1.0325	1.5%	1.631	58.0
3	1.251	1.139	1.195	6.6%	1.453	21.6
6	1.013	1.013	1.013	0	1.675	65.3
7	1.07	1.17	1.12	6.3%	1.88	67.9
8	1.356	1.147	1.252	11.8%	2.521	101.4
10	1.371	1.199	1.285	9.4%	2.418	88.17
Mean	...	...	1.133	...	1.90	66.9
SEM	...	...	0.042	...	0.155	9.5
Between-subject CV	...	...	9.9%		21.5%	...
Within-subject pooled CV	...	...	...	7.2%	...	...

Case no.	Minimal Steady-State Concentration (μg/ml)				Maximal Steady-State Concentration (μg/ml)	Percent Increase
	t = 24 hr	t = 36 hr	Mean	CV		
			Quinidine Gluconate			
1	1.021	0.723	0.87	24.1%	1.743	100.3
2	0.948	0.849	0.899	7.8%	1.508	67.7
3	1.078	0.871	0.974	15.0%	1.285	31.9
6	0.789	0.788	0.7885	0.1%	1.238	57.0
7	0.623	0.797	0.710	17.3%	1.126	58.6
8	1.35	0.97	1.16	23.3%	2.42	109.0
10	0.866	0.878	0.87	0.9%	1.444	65.9
Mean	...	...	0.896	...	1.538	70.1
SEM	...	...	0.054	...	0.166	10.0
Between-subject CV	...	...	...	15.96%	28.5%	...
Within-subject pooled CV	...	...	...	15.6%	...	...

CV = coefficient of variation = standard deviation/mean, expressed in percent; SEM = standard error of the mean.

area under the 30 hour serum concentration curve (AUC-30), averaged 86.0 and 76.5 percent, respectively (Table II). Both values were significantly smaller than 100 percent, but the difference between the two preparations did not reach significance (paired $t = 0.99$). Based on the dose-corrected 48 hour urinary excretion value (UE-48), the systemic availability of quinidine sulfate averaged 83.7 percent and that of quinidine gluconate was 73.6 percent. Again, both values were significantly less than 100 percent. For this measure of bioavailability, the difference between the two preparations was significant ($P < 0.05$). The findings indicate that the systemic availability of both oral quinidine preparations is significantly less than 100 percent. The availability of quinidine gluconate is about 10 percent less than that of the sulfate preparation.

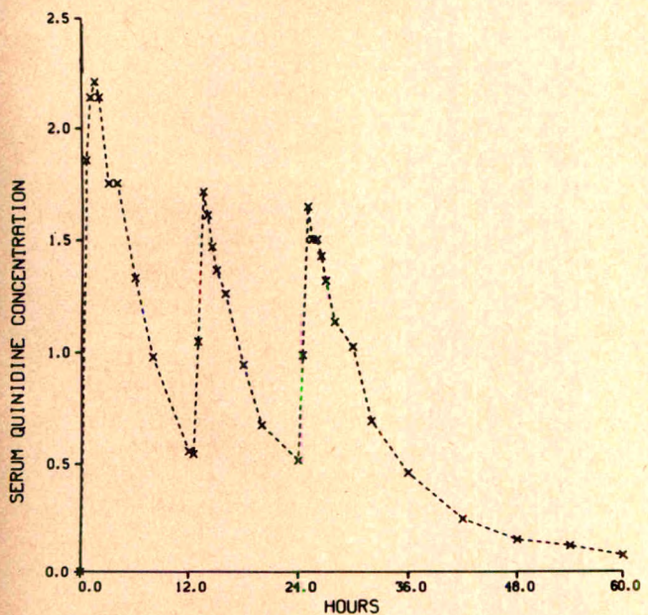


FIGURE 3. Subject 8. Serum quinidine concentrations (μg/ml) after ingestion of 600 mg of quinidine sulfate at time 0, followed by 300 mg at 12 and 24 hours.

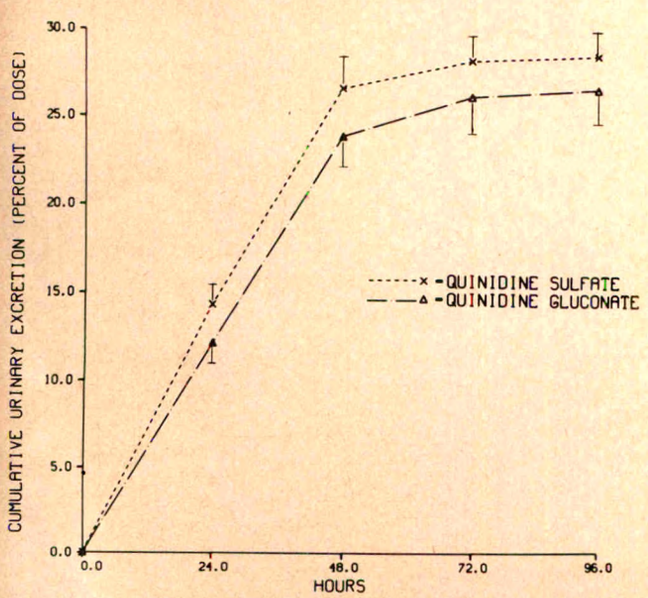


FIGURE 4. Cumulative urinary excretion of quinidine during 96 hours after the start of the multiple dose trials with quinidine sulfate or gluconate. Each point is the mean (± standard error) for all subjects at corresponding times.

Second Study

Interdose fluctuation in serum concentrations: Figure 2 shows mean serum quinidine concentrations during the simulated long-term dosage with quinidine sulfate and gluconate. The minimal steady state serum level during the quinidine sulfate trial averaged 1.13 (± 0.11) μg/ml; the between-subject coefficient of variation was 99.9 percent, and the pooled within-subject coefficient of variation was 7.2 percent (Table III). The maximal steady state concentration averaged 1.90 (± 0.16) μg/ml, with a between-subject coefficient of variation of 21.5 percent. The mean interdose fluctuation in serum concentration, calculated as the percent difference between the maximal and the minimal concentration, averaged 66.9 (± 9.5) percent (Table III). Administration

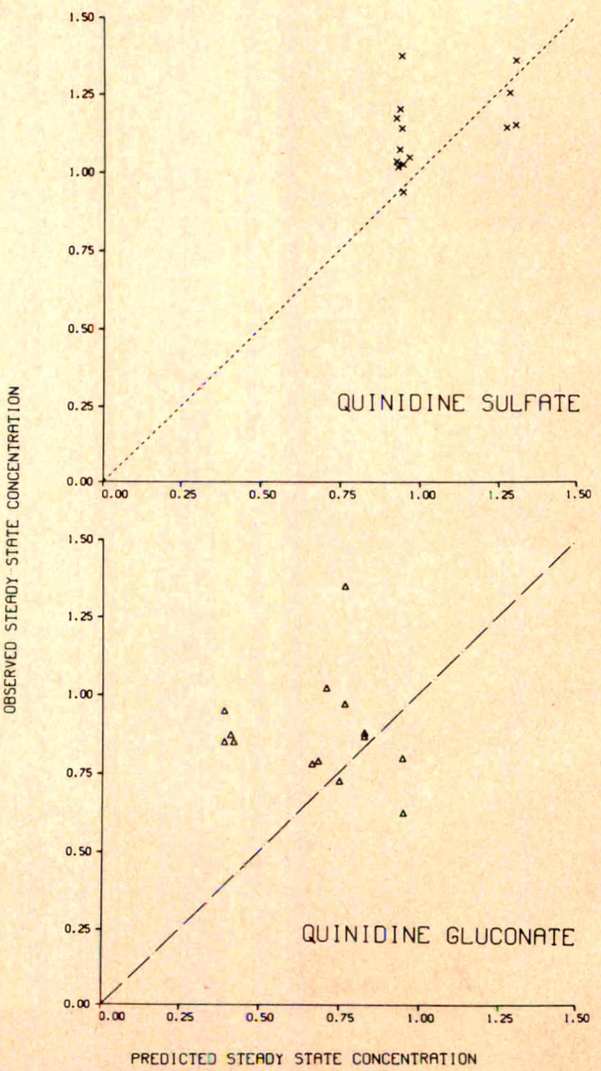


FIGURE 5. Observed and predicted minimal steady state serum quinidine concentrations (μg/ml) during the multiple dose trials with quinidine sulfate (**above**) and gluconate (**below**).

of quinidine sulfate to Subject 8 on the every 12 hour schedule caused large interdose fluctuations in serum levels (Fig. 3). The peak concentration was about three times higher than the minimal level.

During the quinidine gluconate trial, the minimal steady state serum level averaged 0.90 (± 0.05) μg/ml. The between- and within-subject coefficient of variation values were 16.0 and 15.6 percent, respectively. The maximal steady state serum level averaged 1.54 (± 0.17) μg/ml, with a between-subject coefficient of variation of 28.5 percent. The interdose fluctuation during the quinidine gluconate trial averaged 70.1 (± 10.0) percent, which was not significantly different (paired t = 0.45) from that observed during the quinidine sulfate trial.

The findings indicate that interdose fluctuation in steady state serum concentrations for quinidine gluconate given every 12 hours is nearly identical to that for quinidine sulfate given every 6 hours. Variation between subjects in steady state serum levels, for either of the two preparations, was about the same as the within-subject variation. However, both within and between subject variability in minimal steady state concentrations tended to be larger for the gluconate preparation than for the sulfate.

Systemic availability: The dose-corrected area under the steady state serum concentration curve during the quinidine gluconate trial (0.047 ± 0.005 units) was smaller than that observed during the sulfate trial (0.052 ± 0.004 units), but the difference was not significant (paired t = 1.35). Cumulative 96 hour urinary excretion of quinidine (Fig. 4) also was slightly higher during the sulfate trial (28.5 ± 1.6 versus 26.5 ± 2.0 percent of the dose), but the difference was not significant (paired t = 1.83). The findings are consistent with those of the single dose study, indicating that quinidine sulfate has about 10 percent greater systemic availability than quinidine gluconate.

Observed versus predicted concentrations: For both preparations, observed minimal steady state serum concentrations deviated considerably from those predicted by computer based upon the single dose study (Fig. 5). Observed and predicted concentrations were not significantly correlated during either the quinidine sulfate (r = 0.45) or quinidine gluconate (r = −0.12) trials. Deviation from the line of identity tended to be greater for gluconate than for sulfate (paired t = 1.09), but the difference was not significant. Figure 6 shows observed and predicted serum quinidine concentrations during the entire study for Subject 6, from whom the largest number of blood samples was drawn.

Discussion

This study assessed the pharmacokinetics of two oral quinidine preparations after single and multiple doses administered to healthy volunteers. The findings cannot be directly extrapolated to patients receiving quinidine for the treatment of cardiac arrhythmias. Such patients often are elderly, have compromised cardiovascular status and are taking other drugs. All of these factors can potentially influence the absorption, distribution and elimination of quinidine. Nevertheless, our results provide a framework for understanding the pharmacokinetic differences between quinidine sulfate and gluconate and the implications of these differences for antiarrhythmic therapy.

Systemic availibility of quinidine preparation: The single dose study indicated that the systemic

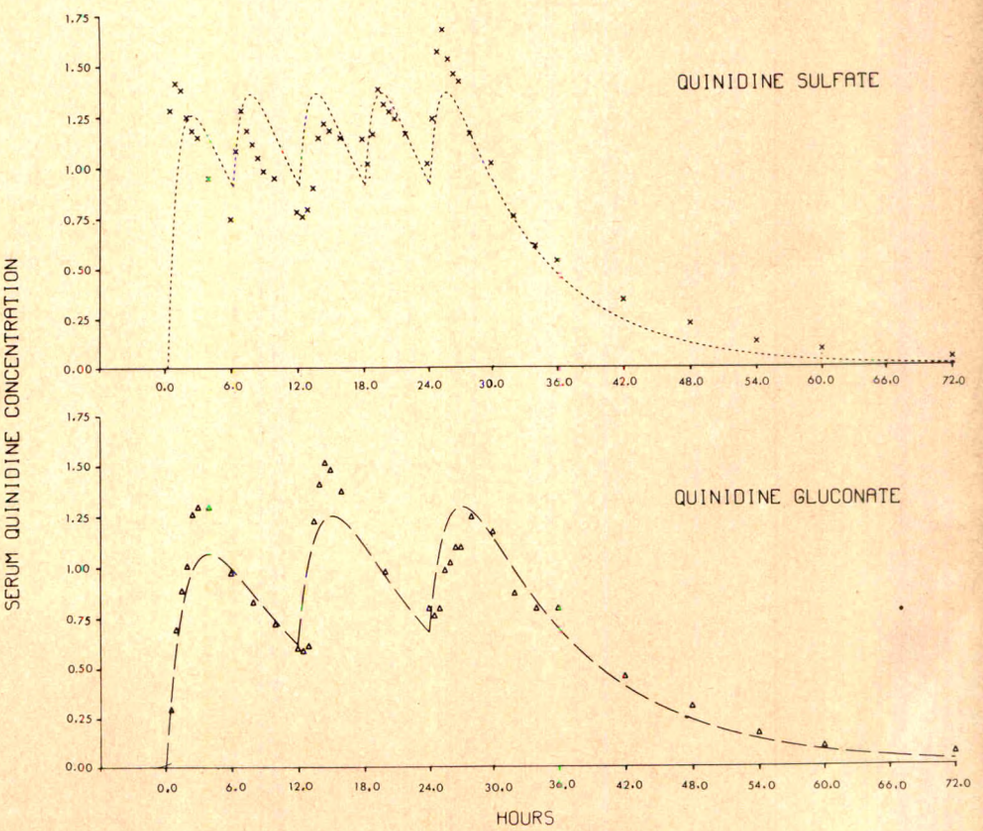


FIGURE 6. Subject 6. Observed (**crosses and triangles**) and predicted (**dashed lines**) serum quinidine concentrations (μg/ml) during the multiple dose trials with quinidine sulfate (**above**) and gluconate (**below**).

availability of both oral quinidine preparations is significantly less than 100 percent. The apparent systemic availability of quinidine sulfate averaged about 85 percent, and that of quinidine gluconate was about 75 percent. Similar findings were reported by others.[14–16] Studies of the renal and extrarenal clearance of intravenous quinidine indicate that the incomplete systemic availability of oral quinidine, regardless of the dosage form, is at least partly due to first pass hepatic metabolism.[1,14] The 10 percent difference in bioavailability between the two oral preparations probably reflects less complete gastrointestinal absorption of the gluconate salt. The clinical significance of the difference is not established. It seems likely that unpredictable variations within and between subjects in the rate and completeness of absorption of both preparations, as well as variations in physiologic status and clinical response, would render a 10 percent difference in systemic availability relatively unimportant.

Rate of absorption of quinidine preparations: In contrast to the small difference between oral preparations in apparent completeness of absorption, large differences existed in the rate of absorption. Peak serum quinidine levels after single oral doses of quinidine gluconate averaged 60 percent lower and were achieved 2 hours later than with quinidine sulfate. The mean apparent first order absorption half-life for quinidine gluconate was about 60 minutes, indicating that the absorption process would require 3 to 4 hours to be 90 percent complete. As expected, there was no significant difference between the two quinidine preparations in the apparent rate of elimination once the absorption phase was complete.

Achievement of steady state concentrations: After initiation of long-term drug therapy with any given maintenance dose, drug accumulation to the steady state condition is more than 90 percent complete after an interval exceeding four times the drug's apparent elimination half-life.[9] In our study, the elimination half-life of quinidine averaged about 6.2 hours, and in no case did it exceed 9.4 hours; furthermore, a loading dose was given to all subjects in both long-term dose trials. Thus the study design, which involved assessment of steady state kinetics 24 hours after the start of treatment, virtually ensured that all subjects were in or very near the true steady state.

Dosage schedule for long-term maintenance therapy: The results of the multiple dose trial generally were consistent with the single dose findings. The apparent bioavailability of quinidine gluconate at steady state level was about 10 percent less than that of quinidine sulfate, based upon the area under the serum concentration curve and cumulative 96 hour urinary excretion value. However, because of the much slower rate of quinidine absorption from the gluconate preparation, interdose fluctuations in serum quinidine concentrations were nearly identical for the two preparations even though quinidine gluconate was given at more widely spaced dose intervals. Administration of quinidine sulfate every 6 hours yielded maximal serum concentrations averaging 67 percent higher than the minimal concentration. For quinidine gluconate given every 12 hours, the maximal concentration averaged 70 percent higher than the minimal concentration. This degree of interdose fluctuation is generally acceptable in clinical practice, suggesting that administration of quinidine gluconate every 12 hours is a feasible dosage schedule during long-term therapy. On the other hand, administration of quinidine sulfate every 12 hours is probably not advisable because it produces large interdose variations in serum levels (Fig. 3). For patients in whom the 67 to 70 percent serum level fluctuation observed with the 6 hourly quinidine sulfate or the 12 hourly quinidine gluconate schedule is unacceptable, administration of quinidine gluconate every 6 or 8 hours would reduce this fluctuation considerably.

Maintenance of serum concentration during maintenance therapy: Accurate prediction of steady state serum concentrations in individual subjects based upon single dose pharmacokinetics was not achieved with either quinidine preparation. Observed steady state serum levels deviated considerably from the predicted values, suggesting within-subject dose to dose variations in quinidine pharmacokinetics. Deviation of observed from predicted values tended to be greater during the quinidine gluconate trial. Furthermore, both within and between subject variation in minimal steady-state concentrations was greater with quinidine gluconate than with quinidine sulfate. The slower rate of quinidine absorption from the gluconate preparation appears to be associated with greater variability in absorption kinetics. The clinical importance of these variations is not established, but they emphasize that monitoring of serum concentrations during maintenance therapy with any oral quinidine preparation is advisable for patients requiring tight control.

Acknowledgment

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Propranolol Rebound—A Retrospective Study

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To assess the effects of sudden withdrawal of propranolol on inpatients with coronary artery disease, 102 patients admitted for cardiac catheterization were evaluated. Criteria for inclusion in the study were angiographically documented coronary artery disease, propranolol therapy at a mean daily dose of at least 80 mg and abrupt discontinuation of propranolol therapy before catheterization. There were 55 patients (mean age 52.5) who discontinued propranolol therapy (mean daily dose 127 mg) and a control group of 47 patients (mean age 53) who continued to receive propranolol (mean daily dose 143 mg). The criteria for morbidity were death, myocardial infarction or change in pain pattern. In the withdrawal group there were no deaths, one myocardial infarction judged to be related to catheterization and only one instance of a change in pain pattern. Thus, propranolol rebound appears to occur infrequently among hospitalized patients with reduced activity.

Since 1973 when Slome[1] described two patients who had a myocardial infarction after the abrupt discontinuation of propranolol therapy for angina pectoris, the entity of propranolol rebound has been universally accepted. It has been defined as an increase in the number or severity of anginal attacks or the appearance of unstable or crescendo angina, myocardial infarction or death after abrupt cessation of administration of the beta adrenergic blocking drug propanolol. At our center it was common practice (before publication of these reports) to discontinue propranolol therapy 48 hours before cardiac catheterization to obtain more accurate assessment of left ventricular function. We believed that little morbidity or mortality was associated with this practice. To analyze objectively this clinical impression we undertook this retrospective analysis.

Materials and Methods

A total of 916 charts of patients who underwent cardiac catheterization and selective coronary arteriography from January 1973 to June 1975 were reviewed. Criteria for inclusion in the study were documented coronary artery disease (stenosis of 70 percent or greater of luminal diameter of at least one major coronary artery) and propranolol therapy for angina pectoris with a minimum dose of 80 mg for at least 3 months before long-term hospital admission. A total of 102 patients met these criteria.

Strict criteria for propranolol rebound were established: (1) a change in pain pattern (frequency, ease of production or number of episodes): (2) myocardial infarction (diagnostic electrocardiographic or enzyme abnormalities, or both); and (3) death. The data were obtained from physician progress notes, nurses' notes, medication sheets and order sheets. Catheterization reports on all patients were reviewed for severity of stenosis and number of vessels involved.

Patients were separated into two groups: Group I, 55 patients who discontinued propranolol abruptly in the hospital and Group II, 47 patients who continued to take the drug throughout their admission (Table I). Group I included

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47 men (mean age 53.2 years, range 34 to 68) and 8 women (mean age 49.5 years, range 38 to 59). The mean daily dose of propranolol was 127 mg (range 80 to 320). The duration of withdrawal from the drug was 1 to 11 days (mean 3.3) in 47 patients; propranolol therapy was not restarted in 8 patients who underwent saphenous vein coronary bypass grafting surgery shortly after catheterization. Group II, 47 patients who continued to take propranolol, included 41 men (mean age 53.2 years, range 40 to 71) and 6 women (mean age 51.7 years, range 44 to 60). The mean daily dose of propranolol in this group was 143 mg (range 80 to 320). Approximately 50 percent of each group had documented triple vessel coronary artery disease.

Statistical analysis was performed using the nonpaired *t* test and chi square with a 2 by k contingency table.

Results

Fifteen (27 percent) of the 55 patients who had abruptly discontinued propranolol therapy had episodes of chest pain in the hospital. In only one patient were these judged to represent a change in pattern of pain (Table I). Thirteen (28 percent) of the 47 patients in the control group had chest pain, but no patient showed a change in pattern of pain. One patient who discontinued propranolol therapy had an acute myocardial infarction that was judged to be catheterization-related because it followed selective coronary arterial injection, ventricular dysrhythmia and hypotension. There was no death in the group that discontinued use of propranolol, and no myocardial infarction or death occurred in the control group.

TABLE I

Patient Characteristics and Morbidity in Patients With and Without Propranolol Withdrawal

	Patients With Propranolol Withdrawal*	Patients Without Propranolol Withdrawal*
Patients (no.)	55	47
Men (no.)	47	41
Mean age and range (yr)	53.2; 34–68	53.2; 40–71
Women (no.)	8	6
Mean age and range (yr)	49.5; 38–59	51.7; 44–60
Mean daily propranolol dose (mg)	127	143
Coronary artery disease (no. of patients and %)		
Single vessel disease	14 (25%)	5 (11%)
Double vessel disease	12 (22%)	19 (40%)
Triple vessel disease	29 (53%)	23 (49%)
Morbidity (no. of patients and %)		
Chest pain in hospital	15 (27%)	13 (28%)
Change in pain pattern	1 (2%)	0
Myocardial infarction	1† (2%)	0
Death	0	0

* There are no statistically significant differences between the groups with and without propranolol withdrawal.
† Judged catheterization-related.

Discussion

The two groups were well matched in number, age and sex of patients, daily dosage of propranolol, frequency of chest pain in the hospital and extent of coronary artery disease. The only difference related to one patient whose pattern of chest pain changed after discontinuation of propranolol (a 2 percent incidence rate of rebound according to our criteria). This patient's condition stabilized quickly when drug treatment was restarted. In this retrospective view inhospital morbidity from abrupt discontinuation of propranolol appeared to be virtually nonexistent. There were no deaths.

Incidence of propranolol rebound: The published data on propranolol rebound include only one controlled prospective study. Miller et al.[2] reported, as part of a double blind efficacy study of propranolol for angina pectoris, a 50 percent incidence rate of rebound phenomena. Ten of 20 of their patients had evidence of "rebound" (intermediate syndrome in 3, fatal myocardial infarction in 1, sudden death in 1, ventricular tachycardia in 1 and increased angina in 4). Their study was conducted in outpatients who underwent stress testing as part of the study. Shand,[3] in an editorial accompanying this report, noted Ayerst Laboratory data revealing a less than 3 percent incidence rate of propranolol rebound. All other studies have been case reports. Alderman et al.[4] reported on six patients; three had a myocardial infarction, one died suddenly and two had exacerbation of their angina which returned to previous levels on resumption of propranolol therapy. Four of these patients were part of a controlled efficacy study with exercise testing as part of the protocol.[5] Mizgala and Counsell[6] reported on 15 acute coronary events in 14 patients receiving propranolol; in 9 of these patients anginal symptoms had increased before cessation of propranolol therapy.

Mechanism of propranolol rebound: Although there is universal agreement that propranolol rebound does occur, its mechanism is unknown.[6–9] Possible explanations include increased sympathetic tone becoming unmasked upon cessation of beta adrenergic blockade; a shift of the oxyhemoglobin dissociation curve[10,11] (a favorable rightward displacement occurs with propranolol therapy) and a subtle adverse alteration in oxygen affinity for hemoglobin; increased platelet aggregation[12–14] (propranolol may diminish platelet aggregation); reactivation of the renin-angiotension aldosterone mechanism; progression of disease without induction of myocardial injury[15]; or continuation after withdrawal of propranolol of the same level of exercise stress achieved during propranolol therapy, thus worsening the coronary oxygen supply-demand equation. It is possible that this last explanation explains the dramatic difference between our results and those of Miller et al.[2]

Therapeutic implications: We conclude that there is little risk (2 to 3 percent) that the propranolol rebound syndrome will develop in patients being treated for symptomatic coronary artery disease if abrupt discontinuation of propranolol therapy is mandated by

clinical circumstances (for example, the need for immediate surgery) provided physical activity is significantly curtailed. Psychologic stress in patients preparing to undergo open heart surgery cannot be quantitated, and this must be considered in relation to patients who will have abrupt withdrawal of propranolol. Thus, until more is learned about preventing such stress it seems prudent to reduce the drug dosage of propranolol for several days before its administration is completely stopped.

Acknowledgment

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The interview excerpted here was conducted with Dr. Bertram Pitt, M.D., Professor in Internal Medicine and Director of the Cardiovascular Division, University of Michigan Medical Center, Ann Arbor, Michigan. Dr. Pitt was formerly Professor of Medicine, Johns Hopkins University.

Q. How do you perceive the role of nuclear cardiology in practice today?

A. I think it's still going through an evolving stage. There are parts that are still in clinical investigation and parts that could be considered clinical practice. There are a number of situations in the coronary care unit where the ability to measure ventricular function and to evaluate therapeutic agents is proving to be useful. We can now quickly determine whether a given agent is helping or not and, therefore, use therapeutic agents more effectively.

Q. What, in your opinion, are the advantages of nuclear cardiology for the evaluation of patients with coronary artery disease?

A. The first advantage with these tracer techniques is that we have the ability to look at a variety of functions. We can determine whether or not ischemia is present using thallium 201; we can determine whether or not an acute infarction has occurred; and we can determine the effects of ischemia or infarction on overall and regional ventricular function. Secondly, to evaluate ventricular function by standard contrast angiography, we make several assumptions as to ventricular geometry which may not be valid in patients with coronary artery disease and disordered wall motion. Using the current radioactive tracer techniques, we can determine a time/activity curve. From this we can determine overall and regional ventricular function without making any assumption as to ventricular geometry. A third advantage is that the tracer procedures are noninvasive, easily repeatable, less risky and somewhat less expensive.

Q. What are the concerns affecting universal acceptance of nuclear cardiology?

A. I think at the moment the major impediment to its use is lack of familiarity on the part of many physicians—under what circumstances are the techniques helpful in solving clinical problems and what are their limitations. I think it is essential that if these techniques are going to be properly used, given the training of cardiologists and nuclear specialists, they must be done as a team effort between nuclear medicine and cardiology.

Q. Will the trend toward nuclear cardiology as a technique in surgical follow-up continue to grow?

A. I think we're going to see more and more pre and post-operative nuclear cardiology studies in patients undergoing coronary artery vein bypass graft surgery. In the pre-operative evaluation, these techniques appear useful in detecting ischemia and giving some idea as to its location and extent. These pre-operative studies serve as a baseline for subsequent post-operative studies.

Q. Are there enough programs available to train physicians in nuclear cardiology?

A. There is a tremendous need at the moment for a new generation of physicians that have cross-disciplinary training. Today, though, as I mentioned earlier, the team approach is essential.

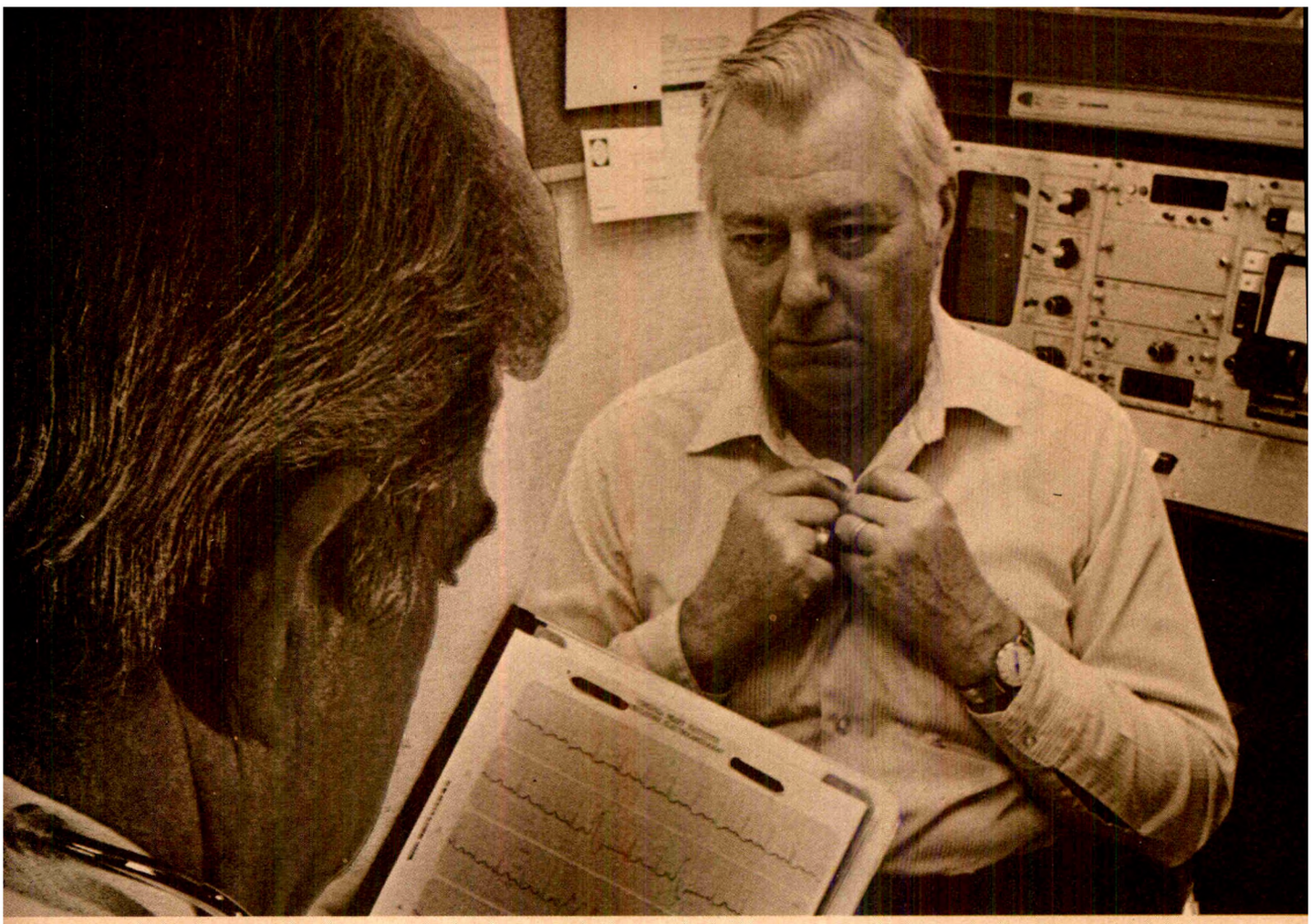
Q. Of what immediate value is nuclear cardiology to patients admitted to coronary care units with a suspected myocardial infarction?

A. I think that the evaluation by nuclear cardiology techniques to determine whether or not a patient has acute infarction is going to be extremely valuable. Once it has been established that the patient has infarction, these techniques will be used to predict survival. These studies can be done right at the patient's bedside in the coronary care unit.

For the complete transcript of this interview with Dr. Pitt, write Inner-View, General Electric Company, Medical Systems Division, P.O. Box 414 (Mail Code W-504), Milwaukee, WI 53201.

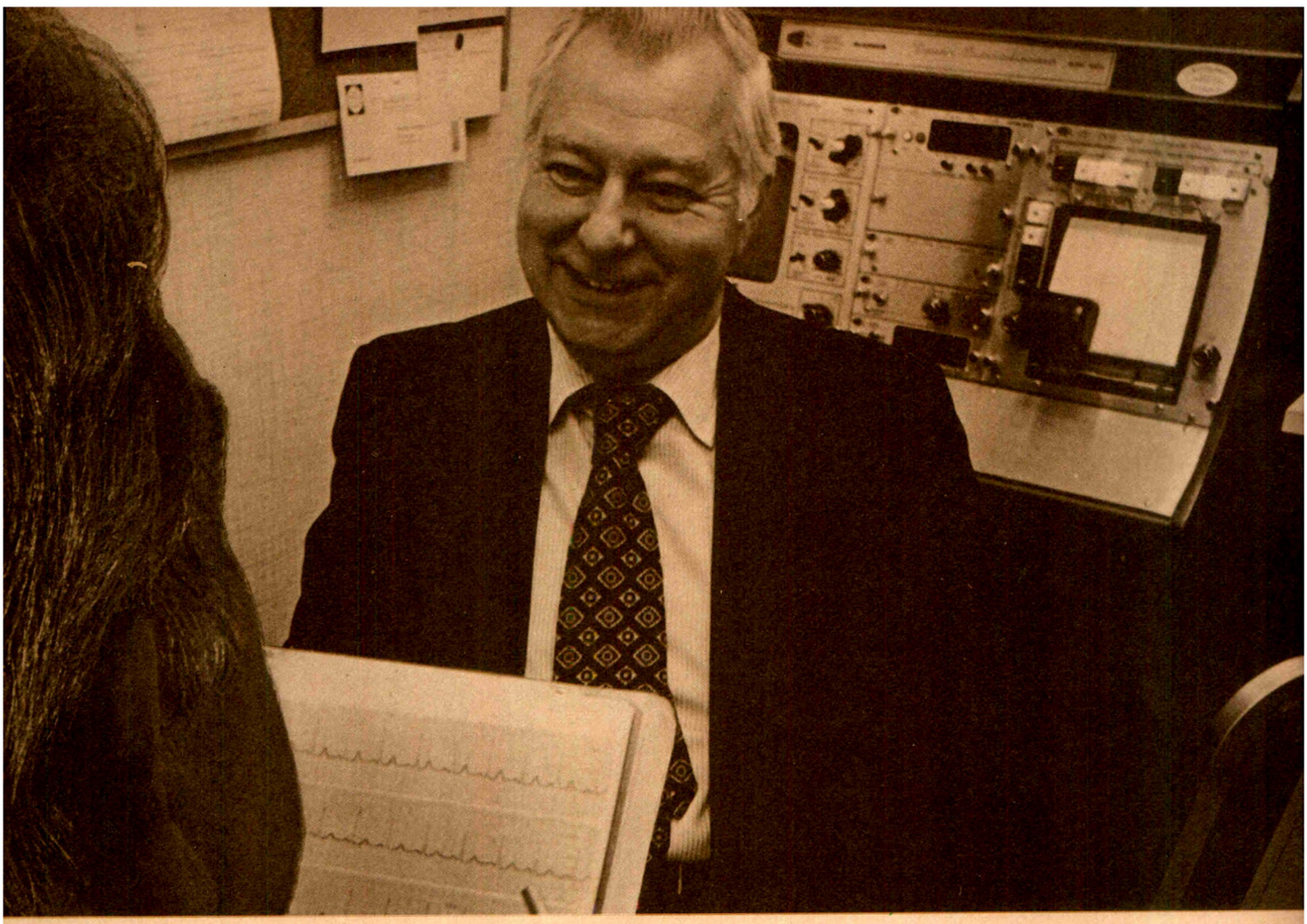
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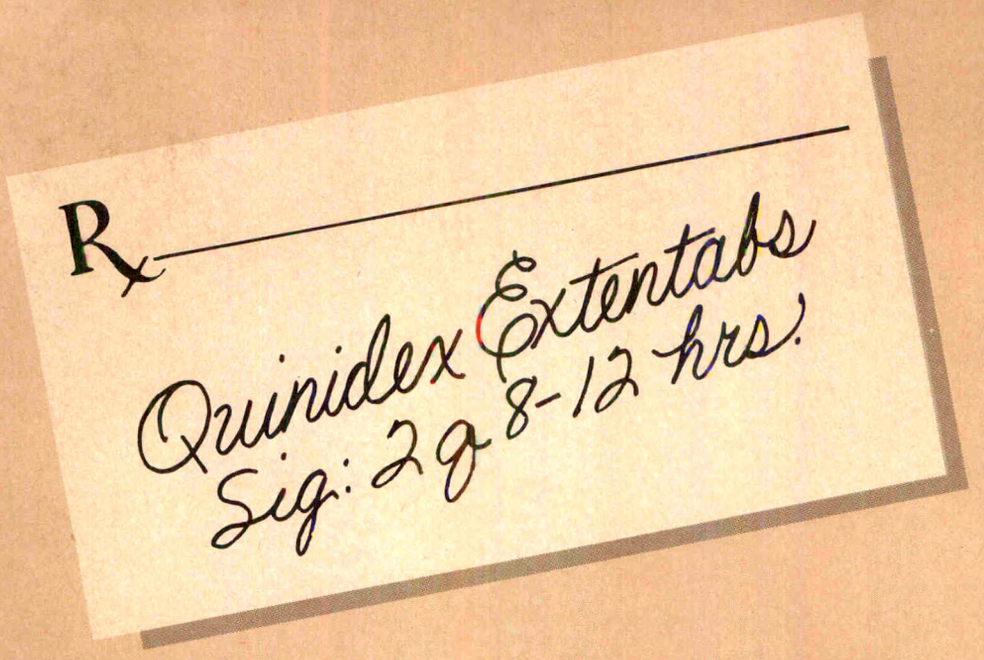
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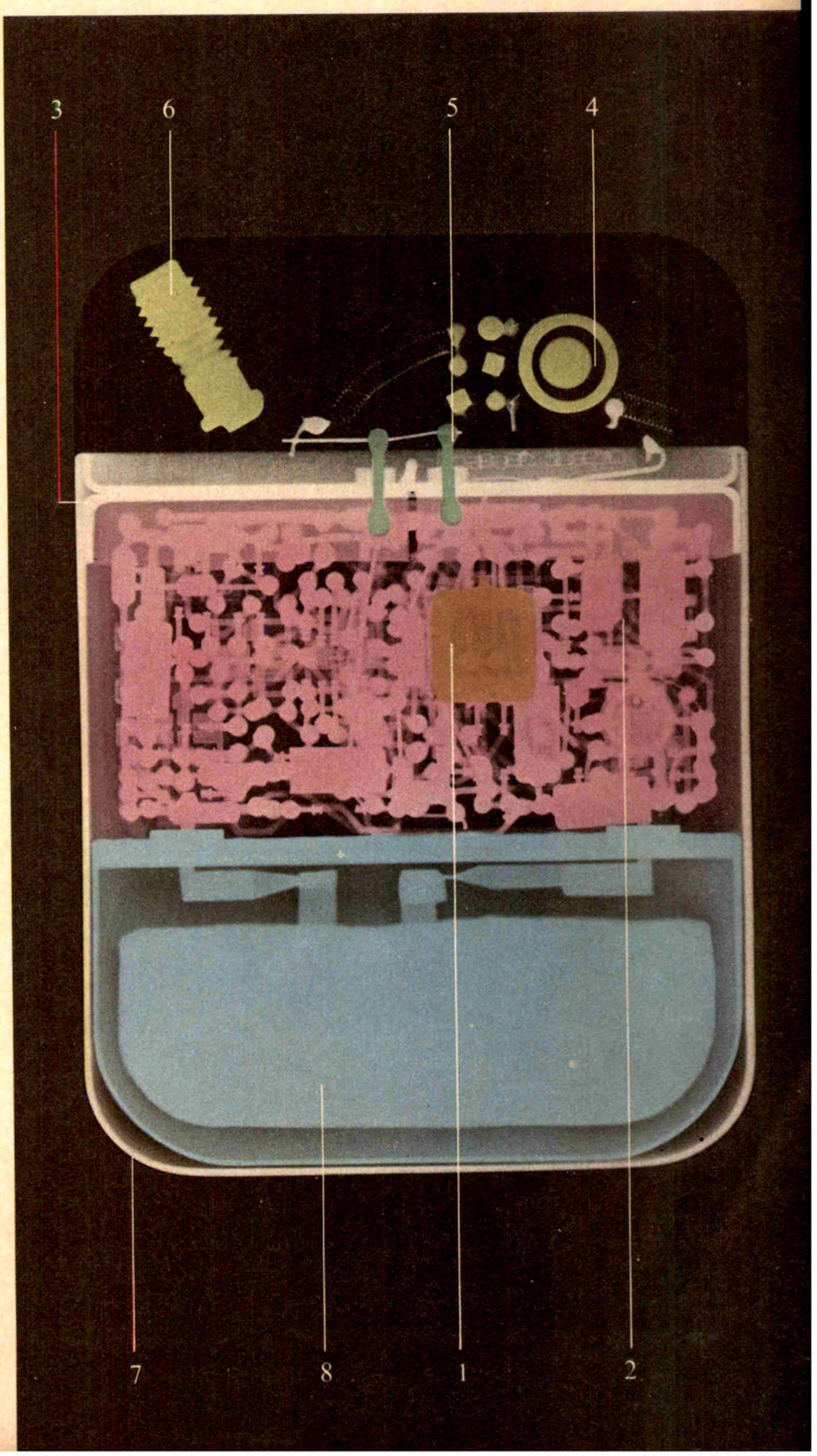
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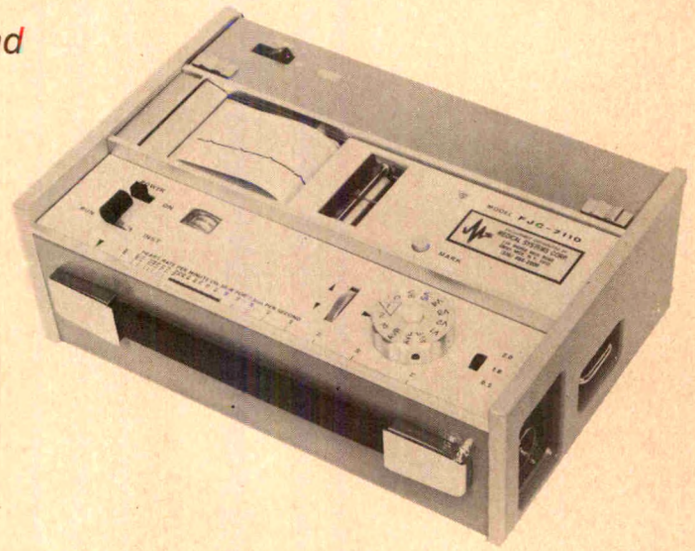
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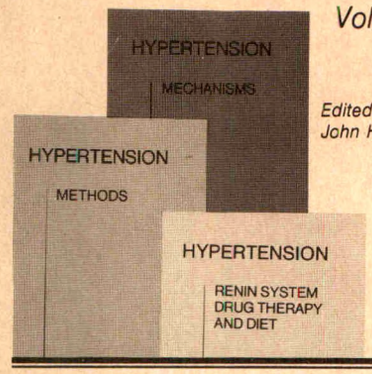
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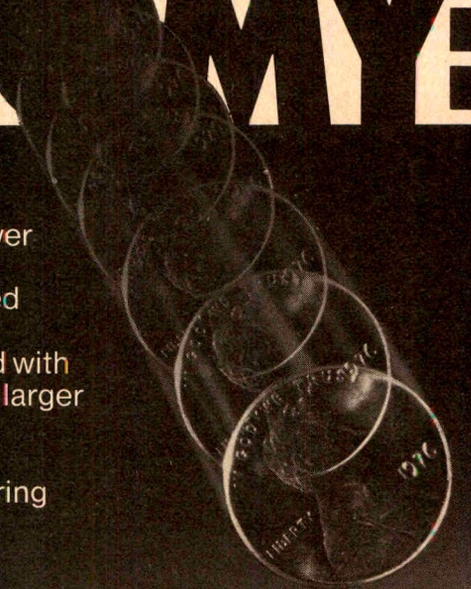
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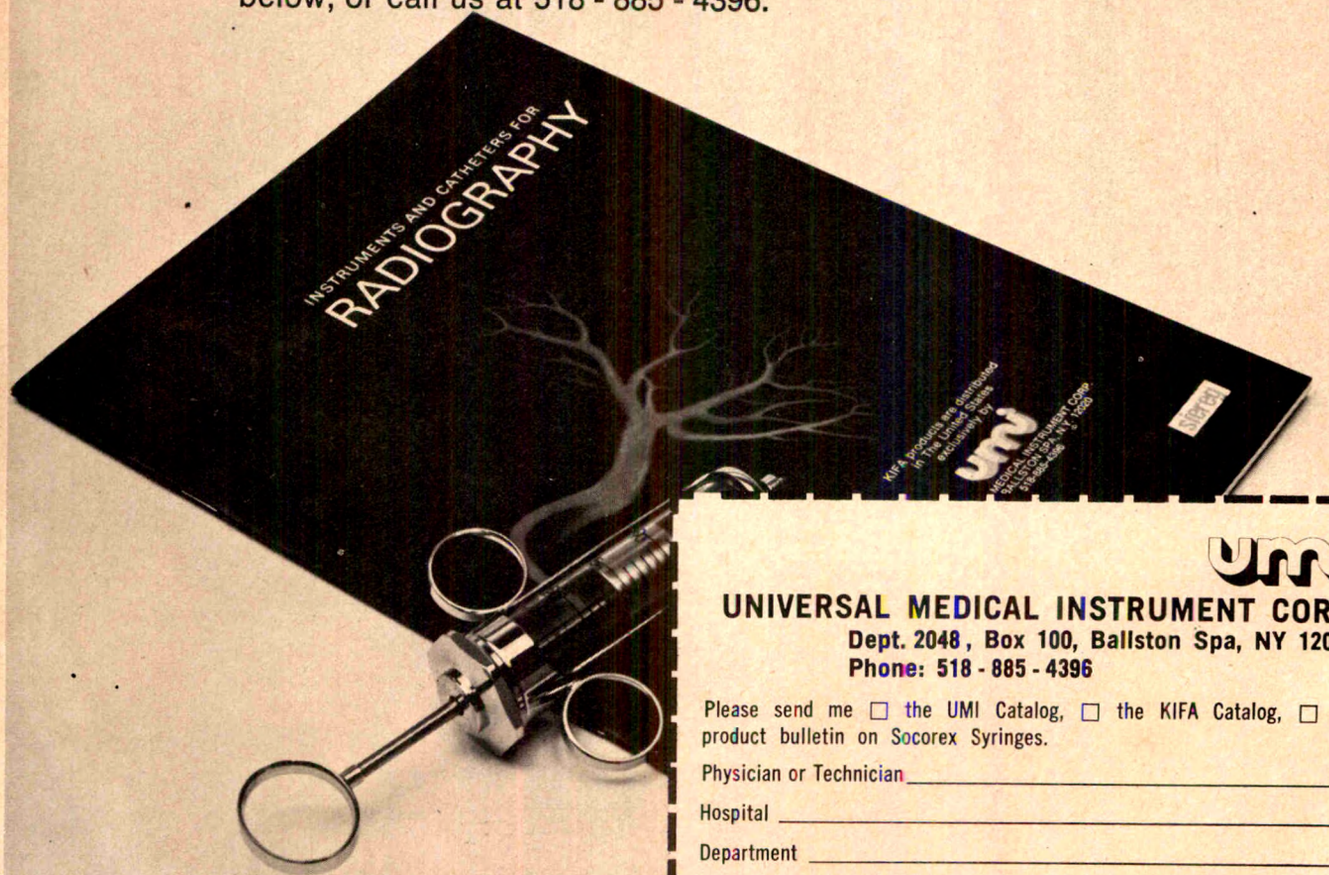
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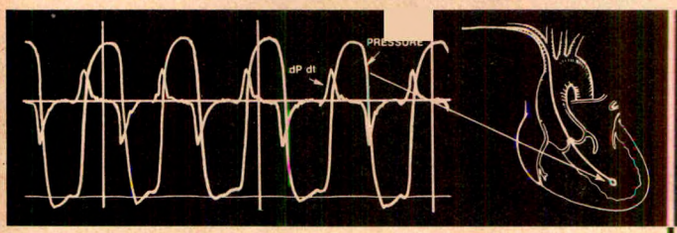
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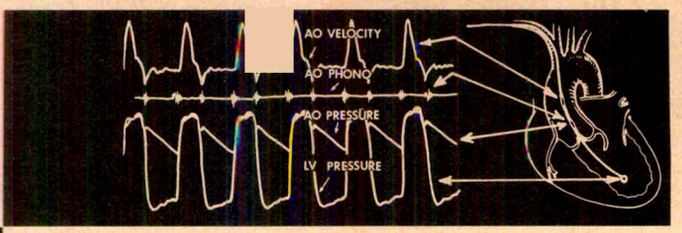
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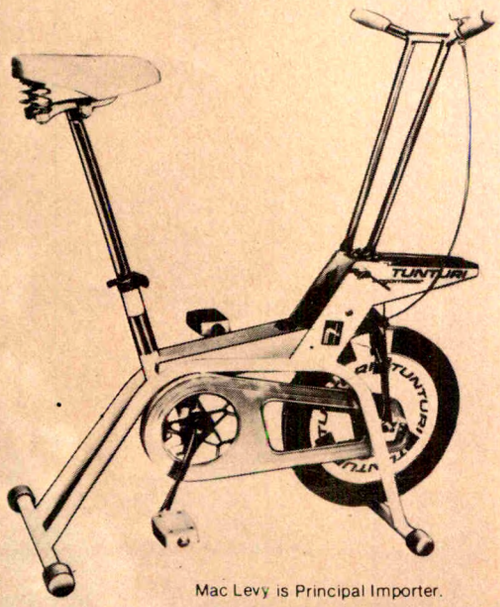
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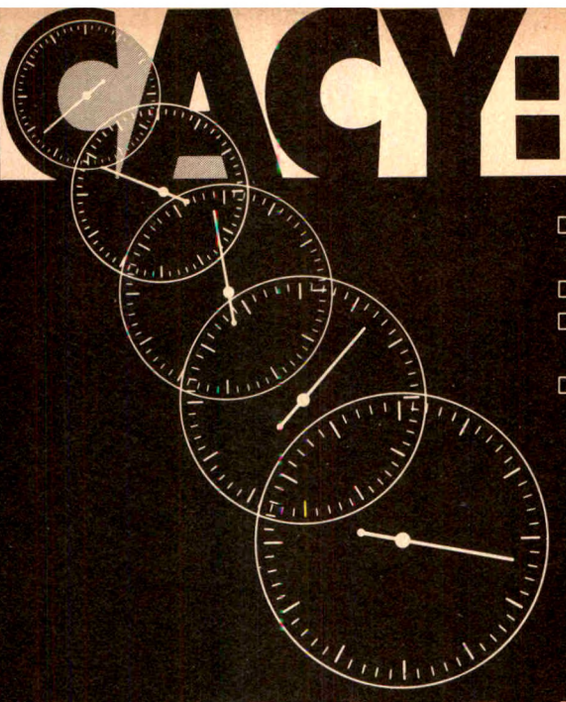
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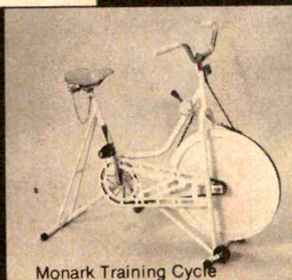
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Effusive-Constrictive Hemodynamic Pattern due to Neoplastic Involvement of the Pericardium

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Eight patients with metastatic malignancy of the pericardium who demonstrated the hemodynamics of subacute effusive-constrictive pericarditis were studied. All patients had clinical evidence of cardiac tamponade due to malignant pericardial effusion and were referred for therapeutic pericardiocentesis. In six in whom pericardiocentesis was successfully performed, right atrial pressure remained elevated after pericardiocentesis and return of the intrapericardial pressure to zero; in these patients, hemodynamic data were initially compatible with tamponade but suggested constriction after removal of the pericardial fluid. In the remaining two patients, echocardiography revealed pericardial fluid, but attempted pericardiocentesis was unsuccessful. In these two patients, the hemodynamic data suggested pericardial constriction; subsequent pathologic examination revealed neoplastic involvement of the visceral pericardium. Thus, subacute effusive-constrictive pericarditis, previously recognized as a complication of tuberculosis or mediastinal radiation, may also be due to metastatic malignancy. The syndrome can readily be demonstrated when right heart catheterization is performed in conjunction with pericardiocentesis.

Cardiac dysfunction due to pericardial disease is usually the result of either chronic constrictive pericarditis or pericardial effusion with tamponade.[1] An intermediate condition in which constriction of the epicardial or visceral pericardium coexists with cardiac tamponade because of effusion between the visceral and parietal pericardial layers was reported by Spodick and Kumar[2] and others[3,4] who pointed out that recognition of this condition may be difficult. Hancock,[5] who termed the entity subacute effusive-constrictive pericarditis, described the hemodynamic findings. He pointed out that the hemodynamic compromise due to this condition is the result of *both* constriction of the visceral pericardium *and* hemodynamically significant pericardial effusion. Its diagnostic hallmark is persistent evidence of cardiac compression *after* removal of the pericardial effusion.[5]

Tuberculosis and mediastinal radiation are the usual clinically recognized causes of effusive-constrictive pericarditis.[5,6] Autopsy studies[7] in patients with metastatic pericardial disease have demonstrated that pericardial effusion combined with visceral pericardial or myocardial invasion by tumor commonly occurs.[7] However, the clinical recognition and hemodynamic documentation of effusive-constrictive pericardial involvement with metastatic malignancy has been infrequently reported.[2]

In this study, we reviewed the hemodynamic findings in eight patients who had undergone pericardiocentesis for suspected malignant pericardial effusion with cardiac tamponade. The results document the occurrence of effusive-constrictive hemodynamics due to pericardial malignancy and suggest that this pattern is not uncommon.

From the Departments of Medicine, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Massachusetts and the University of North Carolina School of Medicine, Chapel Hill, North Carolina. This work was supported by Training Grant HL95727-79, HTB from the U. S. Public Health Service, Bethesda, Maryland. Manuscript received June 8, 1977; revised manuscript received August 1, 1977, accepted September 1, 1977.

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Methods

Patients: The study group consisted of eight patients who had undergone pericardiocentesis for malignant cardiac tamponade at the North Carolina Memorial Hospital between June 1974 and November 1976. None had received irradiation therapy before the pericardiocentesis. The source of the primary tumor was determined from pathologic examination of the tissue obtained at biopsy or at autopsy in each patient. Five patients had carcinoma of the lung, one patient had carcinoma of the breast, one had carcinoma of the cervix and one had histiocytic lymphoma. In seven of the eight cases, pericardial metastases were confirmed with positive findings on cytologic examination of pericardial fluid or at autopsy. The diagnosis was made on clinical grounds in a single patient who had carcinoma of the lung with biopsy-proved metastases; in this patient, results of cytologic examination of the pericardial fluid were negative, but the patient had received no radiation therapy before pericardiocentesis and cultures of the pericardial fluid were negative for tuberculosis.

The 8 patients were selected from a larger group of 14 patients referred to our laboratory for pericardiocentesis because of cardiac tamponade due to malignant involvement of the pericardium. The patients were selected on the basis of demonstrating both pericardial effusion and hemodynamic evidence of visceral pericardial constriction. In six of the eight patients, the diagnosis was confirmed by demonstrating hemodynamics of persistent cardiac compression with increased right atrial pressure (defined in our laboratory as more than 8 mm Hg) after pericardiocentesis.[5] In five of these patients, a normal intrapericardial pressure (0 to 2 mm Hg) was documented after removal of the pericardial fluid. In the other patient (Case 6), intrapericardial pressure was not measured; however, autopsy 16 days after the pericardiocentesis revealed insignificant pericardial effusion with visceral pericardial and myocardial invasion by histiocytic lymphoma.

In two of the eight patients, resting hemodynamic data suggested that pericardial constriction was the primary cause of the cardiac compression.[8,9] In these patients, echocardiography revealed the presence of pericardial effusion, but

TABLE I

Clinical and Hemodynamic Data in Eight Patients With Malignant Effusive-Constrictive Pericarditis

Case no.	State	Pressures (mm Hg) RA	Peri cardium	RV	PA	PAW	Paradoxical Pulse	HR (beats/min)	Pericardial Fluid Amount Removed (cc)	Pericardial Fluid Characteristics	Primary Site of Tumor	Comments
1	R	15	15	35/15	35/15	15	22	114	700	Sanguinous; HCT 20%; + cytologic study	Breast	Alive 11 mo postpericardiocentesis without recurrence. Treatment: intrapericardial chemotherapy
	PP	12	2	35/12	35/15	...	12	116				
2	R	18	...	...	35/18	20	30	105	2,500	Sanguinous; HCT 14%; − cytologic study and TB cultures	Lung	Alive 13 mo postpericardiocentesis without recurrence. Treatment: radiation (no radiation before tamponade)
	PP	10	...	...	36/16	...	5	110				
3	R	23	23	36/24	36/24	24	55	108	700	Sanguinous; HCT 17%; + cytologic study	Cervix	Died 4 mo postpericardiocentesis without recurrence. Treatment: radiation and systemic chemotherapy
	PP	10	0	26/12	26/12	12	10	108				
4	R	25	25	65/25	65/35	35	35	138	350	Sanguinous; HCT 17%; + cytologic study	Lung	Died 1 day postpericardiocentesis. No treatment
	PP	20	2	45/20	45/20	35	10	120				
5	R	24	...	...	...	...	...	120	200	Sanguinous; HCT 5%; no cytologic study	Histiocytic lymphoma	Died 16 days postpericardiocentesis. Treatment: radiation and systemic chemotherapy. Autopsy revealed visceral pericardial tumor with myocardial invasion
	PP	18	...	40/18	40/18	20	...	120				
6	R	18	16	...	...	...	...	115	1,300	Sanguinous; + cytologic study	Lung	Died 1 day postpericardiocentesis. Treatment; pericardial window. Extensive visceral pericardial involvement noted at operation
	PP	10	2	...	...	...	...	100				
7	R	20	...	50/20	50/20	20	...	125	...	...	Lung	Died 1 day postpericardiocentesis. Autopsy revealed tumor encasement with myocardial invasion. No treatment
	PP	...	...	...	...	...	...	125				
8	R	12	...	40/13	40/13	...	...	160	20	Sanguinous; + cytologic study	Lung	Died 2 mo postpericardiocentesis. No recurrence. Treatment: radiation
	PP	...	...	...	...	...	...	...				

HCT = hematocrit; HR = heart rate; PA = pulmonary arterial; PAW = pulmonary arterial wedge; PP = postpericardiocentesis; R = resting; RA = right atrial; RV = right ventricular; TB = tuberculosis; − = negative; + = positive; ... = not obtained.

insignificant fluid was obtained at pericardiocentesis. Subsequent autopsy in one of the patients revealed tumor encasement of the heart with myocardial invasion. In the other patient, cytologic examination of a small amount of pericardial fluid revealed malignant cells.

Cardiac and pericardial catheterization: *Right heart catheterization* was performed before and after pericardiocentesis in each patient. Right heart, systemic arterial and intrapericardial pressures were recorded using fluid-filled catheters and external strain gauge transducers. The transducers were balanced at the level of mid right atrium and this position was ensured before pressures were recorded. A thermistor positioned in the external nares was used to monitor respiration.

Percutaneous catheterization of the pericardial space was performed in the cardiac catheterization laboratory.[8] The pericardial space was entered with a thin-walled, short-beveled, no. 18 needle with use of the subxiphoid approach, and a 0.9 mm diameter guide wire was passed through the needle into the pericardial space under fluoroscopic control. After removal of the needle, a no. 8 French Gensini Teflon® catheter with multiple side holes was passed over the wire into the pericardial space. After removal of pericardial fluid and collection of postpericardiocentesis data, this catheter was usually removed. However, in two patients, the catheter was left in the pericardium for a variable period (6 days in one patient, 16 days in another) for the purpose of further therapy.

Hemodynamic data were evaluated in each patient. Comparisons were made between resting and postpericardiocentesis data in each patient, as well as among patients.

Results

Clinical and hemodynamic data for the eight patients are listed in Table I. All patients were in clinically unstable condition and had a resting tachycardia (seven had sinus tachycardia, one had rapid atrial flutter). Although systolic blood pressure was well maintained, all patients had an abnormal pulsus paradoxus on sphygmomanometry; this finding was confirmed in the four patients whose arterial pressure was monitored during cardiac catheterization (range 22 to 55 mm Hg). All eight patients had hemodynamic evidence of cardiac compression with equalization of right atrial mean, right ventricular end-diastolic and pulmonary arterial diastolic pressures at increased levels. Pulmonary arterial wedge pressure was similarly elevated and equal to right atrial pressure in the five patients in whom it was measured. Intrapericardial pressure was measured in five patients and was increased to the level of the diastolic plateau of the intracardiac pressures in each; in these cases, the intrapericardial pressure was identical to the right atrial pressure before pericardiocentesis.

Hemodynamics before and after pericardiocentesis (six cases): The hemodynamic findings in the six patients in whom pericardiocentesis was successful are illustrated in Figures 1 to 3. After removal of pericardial fluid (the amount obtained ranged from 350 to 2,500 cc), intrapericardial pressure decreased to normal levels,

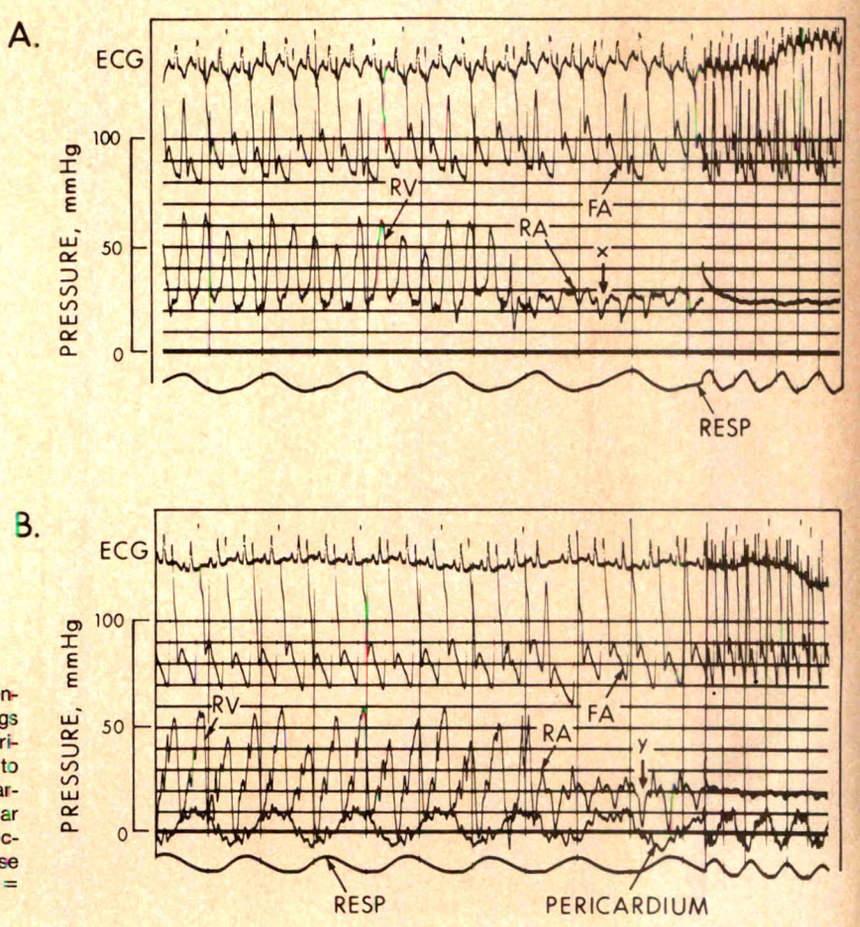


FIGURE 1. Case 4. Femoral arterial (FA) and right ventricular (RV) to right atrial (RA) pullback pressure tracings before (**A**) and after (**B**) pericardiocentesis. After pericardiocentesis and return of pericardial pressure to normal levels, there is loss of the abnormal pulsus paradoxus, but the mean right atrial and right ventricular end-diastolic pressures remain elevated. ECG = electrocardiogram; RESP = respiratory monitor (an increase occurs with inspiration); x = systolic descent and y = diastolic descent of right atrial pressure.

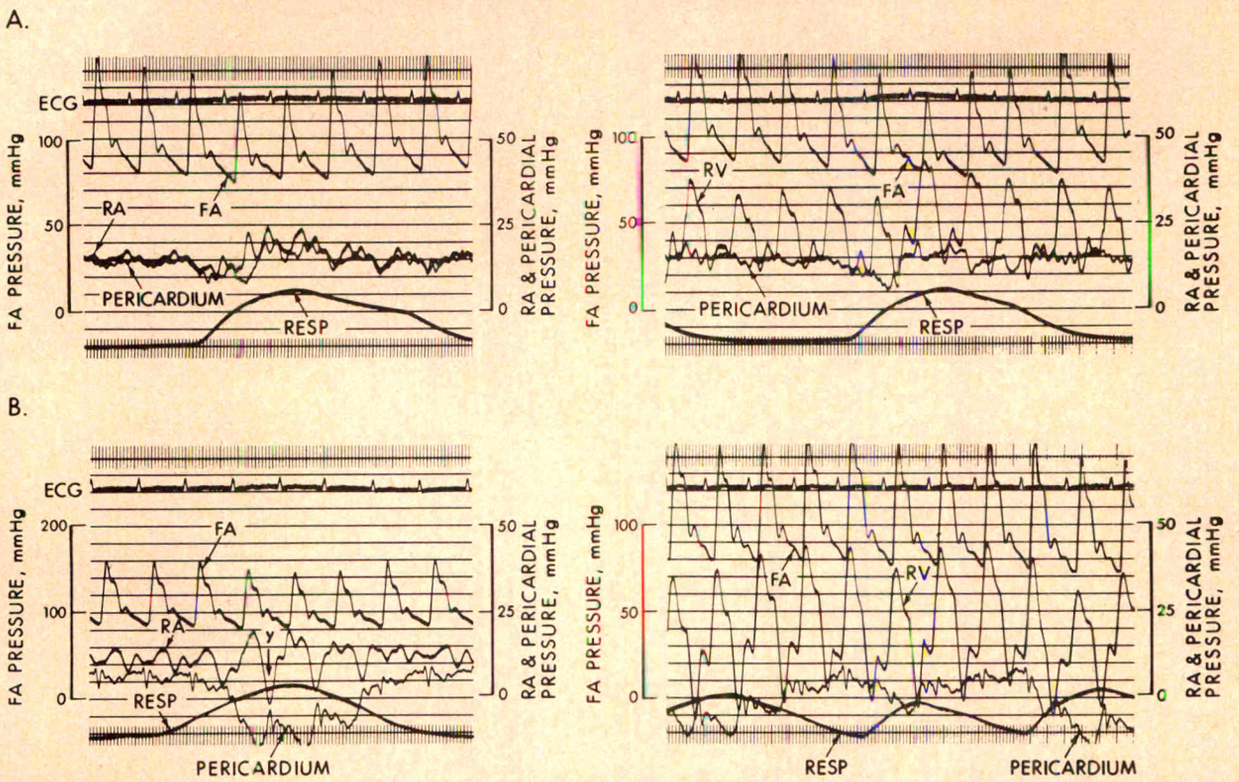


FIGURE 2. Case 1. Femoral arterial (FA), right atrial (RA), right ventricular (RV) and pericardial pressure tracings before (**A**) and after (**B**) pericardiocentesis. **Left panels:** after pericardiocentesis the right atrial pressure remains elevated and develops a prominent Y descent that is accentuated by inspiration. The late inspiratory rise (Kussmaul's sign) persists after pericardiocentesis. **Right panels:** a prominent right ventricular early diastolic pressure dip with a persistently elevated end-diastolic pressure develops after pericardiocentesis. Abbreviations as in Figure 1.

and there was a decrease in the pulsus paradoxus. However, right atrial pressure remained substantially elevated, ranging from 10 to 20 mm Hg. For comparison, an example of the effect of pericardiocentesis on the hemodynamics of simple pericardial effusion and tamponade *without constriction* is illustrated in Figure 4; in this case after pericardiocentesis both right atrial and pericardial pressures returned to normal levels. Before pericardiocentesis, the contour of the right atrial venous wave was most suggestive of cardiac tamponade with a predominant systolic or X descent and a blunted diastolic or Y descent (Fig. 1 to 3). However, in contrast to simple effusion with tamponade, there was absence of the usual decrease in right atrial pressure with inspiration (Fig. 1 and 3). In one patient, there was a late inspiratory rise in right atrial and pericardial pressure with inspiration (Fig. 2). After removal of the pericardial fluid, the contour of the right atrial pressure wave changed significantly, becoming more compatible with constriction. The Y descent of the right atrial pressure became the predominant wave, being greater than or equal to the X descent in all cases (Fig. 1 to 3). The ef-

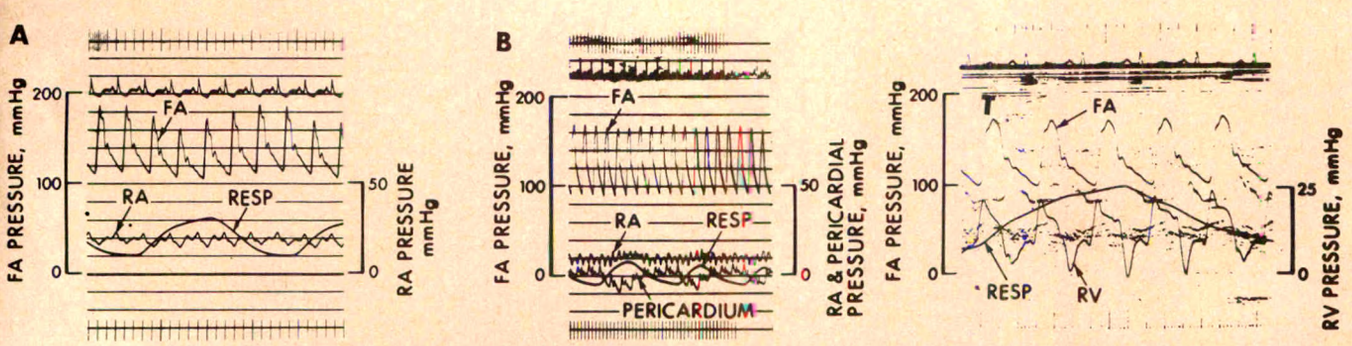


FIGURE 3. Case 3. Femoral arterial (FA), right atrial (RA), right ventricular (RV) and pericardial pressure tracings. **A,** before pericardiocentesis, there is an abnormal pulsus paradoxus and an elevated right atrial pressure with the X descent more prominent than the Y descent. **B,** after pericardiocentesis, the persistently elevated right atrial pressure had prominent X and Y descents and the right ventricular pressure **(bottom right)** assumes the classic "square root" configuration of constrictive pericarditis. Abbreviations as in Figure 1.

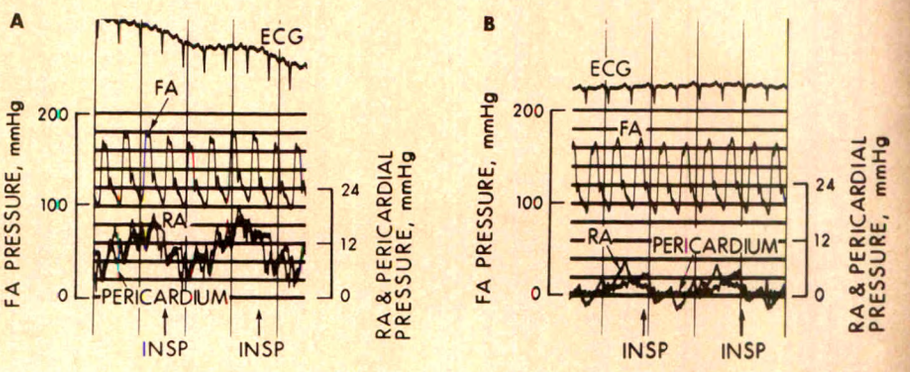


FIGURE 4. Femoral arterial (FA), right atrial (RA) and pericardial pressure tracings before (**A**) and after (**B**) pericardiocentesis illustrating the hemodynamic findings in pericardial effusion with tamponade *without constriction.* In contrast to effusive-constrictive disease (Fig. 1 to 3), both right atrial (RA) and pericardial pressure return to normal after pericardiocentesis. INSP = inspiration, other abbreviations as in Figure 1.

fect of respiration on the right atrial pressure was similar to that before pericardiocentesis although there was a tendency for the Y descent to become more prominent with inspiration after pericardiocentesis (Fig. 1 and 2).

Similar changes were evident in the contour of the right ventricular pressure wave. Before pericardiocentesis, the right ventricular pressure was suggestive of tamponade with an absent or blunted early diastolic pressure dip (Fig. 1 and 2). After pericardiocentesis, the early pressure dip reappeared, but the right ventricular pressure assumed a classic "square root sign" of constriction (Fig. 3).

Hemodynamics after unsuccessful pericardiocentesis (two cases): In the two patients in whom attempted pericardiocentesis removed an insignificant amount of fluid, resting hemodynamic data were distinctly different from those in the other six patients, being more suggestive of constriction than tamponade. The elevated right atrial pressure wave revealed prominent X and Y descents (Fig. 5), and there was a prominent early diastolic pressure dip in the right ventricular pressure tracing in both patients.

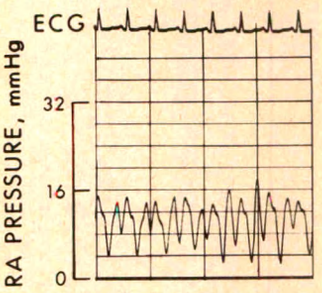


FIGURE 5. Case 8. Right atrial (RA) pressure tracing. Note the increased pressure with prominent X and Y descents suggesting that pericardial constriction was the major hemodynamic abnormality.

Discussion

In recent years, the antemortem diagnosis of carcinoma metastatic to the heart has been made with increasing frequency. Cardiac tamponade due to malignant pericardial effusion is commonly seen and pericardiocentesis with subsequent radiation or cytotoxic drug therapy may provide beneficial palliation.[10,11] However, as Spodick and others[2,12,16] pointed out, the clinical recognition of direct myocardial or visceral pericardial invasion by tumor is difficult. Our major finding in this study is that such involvement is not uncommon and can be hemodynamically demonstrated when right heart catheterization is performed in association with pericardiocentesis in patients with suspected malignant cardiac tamponade.

Effusive-constrictive pericarditis: Six of eight patients demonstrated the hemodynamic features of subacute effusive-constrictive pericarditis previously described by Hancock.[5] The major abnormality was a persistently elevated right atrial pressure after pericardiocentesis when intrapericardial pressure had returned to normal. Before pericardiocentesis, pressure contours were most suggestive of pericardial effusion with tamponade: The right atrial pressure was substantially elevated with a predominant systolic or X descent, the right ventricular early diastolic pressure dip was absent and a significant pulsus paradoxus was present.[8,9] One possible distinctive feature of subacute effusive-constrictive disease before pericardiocentesis was that the right atrial pressure did not decrease with inspiration as is usually seen in tamponade due to effusion alone.[9] After pericardiocentesis and return of pericardial pressure to normal, hemodynamic abnormalities compatible with constriction became evident: The right atrial pressure remained elevated now with a prominent diastolic or Y descent, and the right ventricular pressure developed a prominent early diastolic dip or square root sign with a persistently elevated end-diastolic pressure.[8,9] These hemodynamics suggest that the cardiac compression was the result of both a large pericardial effusion *and* visceral pericardial constriction or myocardial restriction. Thus, removal of the effusion only partially corrected the impaired cardiac function.

Two of the eight patients in our study had pericardial effusion documented with echocardiography, but little or no fluid was obtained at pericardiocentesis. Resting hemodynamics in these patients suggested constrictive pericarditis.[8,9] Subsequent autopsy in one patient revealed encasement of the heart with tumor and extensive myocardial invasion. We conclude that these two patients represented one end of a spectrum of effusive-constrictive involvement, with constriction due to

tumor being the predominant cause of the cardiac dysfunction.

Pathologic basis of cardiac dysfunction: Previous autopsy studies demonstrated the occurrence of tumor metastases to visceral pericardium and myocardium, and provided a pathologic basis for the findings in our eight cases.[2,17,17–24] Thurber et al.[7] formulated the mechanism of cardiac dysfunction from their necropsy evaluation of 55 patients with symptoms due to pericardial metastases. "... A combination of pericardial effusion and myocardial invasion (with tumor) ...", the anatomic correlate of effusive-constrictive hemodynamics, was second to isolated effusion as the most common mechanism of cardiac impairment in their study. Indeed, 55 percent of their patients had myocardial invasion or cardiac constriction, or both, of a sufficient degree to cause cardiac dysfunction.

Prognosis: Because effusive-constrictive hemodynamics are produced when there is visceral pericardial involvement or direct myocardial invasion, it is not surprising that six of our eight patients died within 4 months of the pericardiocentesis. However, two patients survived 11 and 13 months after pericardiocentesis with treatment of their malignancy. The documentation of this type of involvement may be useful clinically as an explanation of persistent symptoms after pericardiocentesis. In this situation, repeat pericardiocentesis or removal of parietal pericardium alone will not provide symptomatic relief.

Implications: It is apparent that impaired cardiac performance due to metastatic disease of the pericardium frequently involves pathophysiologic conditions other than simple pericardial effusion with tamponade. Our eight cases demonstrate that the hemodynamics of effusive-constrictive pericarditis can be uncovered when right heart catheterization is performed in patients with suspected malignant cardiac tamponade. With the recent decline in the incidence of tuberculosis, malignant disease may rival radiation therapy as the most frequent cause of this syndrome.

Acknowledgment

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Coronary Arterial Spasm and Provocative Testing in Ischemic Heart Disease*

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After being moribund for some two decades, the role of coronary arterial spasm in ischemic heart disease has been resuscitated, revived and resurrected.

Reports of patients with Prinzmetal's variant angina (pain at rest with S-T elevation) and no arteriographic evidence of coronary obstruction have been followed by descriptions of several cases of arteriographically documented spontaneous spasm accompanied by pain and S-T elevation. It has rapidly become accepted that coronary spasm causes ischemia in patients with variant angina pectoris, at least in those without significant fixed coronary obstructive lesions. Several reports, including an important study by Heupler et al.[1] in this issue, have now described the use of provocative tests to induce coronary spasm.

Coronary spasm has had a long and fascinating history. Heberden,[2] in addition to his classic description of angina pectoris, reported on a nonexertional form of angina in 1772, and by 1910 Sir William Osler[3] among others was quite impressed with coronary spasm as a cause of ischemia, stating, "I do not know any better explanation for anginal pain." However, when Prinzmetal[4] first established the criteria for variant angina in 1959, his postulation that it was due to coronary spasm was not consistent with the concepts that, in the first era of selective coronary arteriography in the 1960's, appeared to eliminate spasm as a cause of ischemia. Spasm was observed arteriographically in less than 1 percent of cases, was induced mechanically by the catheter itself and even when demonstrable did not cause ischemia. However, the "rediscovery" of spasm has restimulated interest in its possible role in several clinical expressions of ischemic heart disease. It is thus timely to evaluate the evidence relating to (1) the prevalence of coronary spasm as an ischemic stimulus; (2) the cause or causes of coronary spasm; and (3) the uses, limitations and risks of provocative tests to elicit spasm.

Coronary spasm as a cause of ischemia: Clearly the relation between coronary spasm and ischemia is best established in Prinzmetal's variant angina. Guazzi[5] and Maseri[6] and their co-workers have shown that reduction of myocardial blood supply is the primary event responsible for ischemia and several reports have demonstrated arteriographically that spontaneous coronary spasm causes severe reversible ischemia in patients with variant angina and normal arteriograms,[7] as well as in some with significant fixed obstructions.[8,9]

Considerably less attention has been focused on the role of coronary spasm in patients with angina at rest and S-T depression (and not elevation) during ischemia. In the studies of Maseri and Guazzi et al., several patients with no evidence of a prior increase in myocardial oxygen requirements exhibited S-T depression during ischemic episodes.[5,6] Arteriographic studies have shown that although multivessel disease is most frequently found in such patients, there is a subset with no evidence of organic obstructions (19 percent in the series of Scanlon et al.).[7] Thus, there is indirect as well as some direct[8] evidence that spasm may play a role in some patients with angina at rest.

Coronary spasm and myocardial infarction: The relation between spasm and acute myocardial infarction is more speculative because traditional interest has been on coronary thrombosis or plaque hemorrhage. However, these factors may be variable or interrelated; that is, coronary spasm could either initiate hemostasis, re-

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* Editorials published by the Journal reflect the views of the authors and do not necessarily represent the views of the Journal or of the American College of Cardiology.

sulting in thrombosis, or cause plaque rupture with or without hemorrhage. Conversely, plaque disruption or thrombosis, or both, could cause spasm. Several lines of evidence support the role of spasm in at least a subset of patients with myocardial infarction. In 12 of Prinzmetal's original 32 cases of variant angina, infarcts developed, all in the area indicated by the S-T segment elevations during ischemia. Subsequent studies have confirmed this relation, and recently a case was reported in which an anterior infarct occurred 3 months after the arteriographic demonstration of reversible spasm in a normal left anterior descending coronary artery.[11] In addition, there have been increasing reports of patients with a documented myocardial infarction and angiographically normal coronary arteries. A high incidence rate of cigarette smoking has been noted in these patients, a stress that has been related to spasm. In addition, spasm has been pharmacologically induced in the coronary artery subserving the infarct area.[12]

In a recent study by Oliva and Breckenridge,[13] coronary arteriography was performed before and after intracoronary administration of nitroglycerin in 15 patients within 12 hours of acute myocardial infarction. Spasm superimposed on high grade atherosclerotic obstructions was demonstrated in six (40 percent), of these patients occurring in five with infarcts less than 6 hours old. Spasm was also judged a major factor in eight infarcts in the study of Weiner et al.[8] Thus, spasm may play an important role in acute myocardial infarction.

Coronary spasm and sudden death: Sudden death is recognized as the major mode of demise in coronary heart disease but, in spite of general agreement that it results from a catastrophic rhythm disturbance, the arrhythmogenic stimulus is entirely unknown. Whereas the incidence of coronary thrombosis at necropsy in cases of sudden death is small, the role of spasm is largely conjectural. However, severe arrhythmias are frequent in variant angina, and sudden death occurs in about 15 percent of cases. Recently, ventricular tachycardia and fibrillation were observed in a patient with arteriographically documented spasm,[1] and in the series of Weiner et al.,[8] spasm was found in 11 instances of ventricular tachycardia or fibrillation or heart block. A recent study[15] of patients resuscitated from ventricular fibrillation outside the hospital showed that although the majority had advanced atherosclerosis, 4 of 64 patients (6 percent) had only mild (50 percent or less obstruction) coronary lesions. Thus, there is a small subgroup without coronary obstruction sufficient to cause ischemia, and an additional coronary insult such as spasm would presumably be required to result in sudden death.

Causes of coronary spasm: The mechanism of exertional angina seems well established, the increase in myocardial oxygen needs outstripping supply because of fixed coronary obstruction. However, the pathogenesis of angina precipitated by other factors is less clear. Nocturnal angina can be caused by heart failure, but the diurnal variation of the autonomic nervous system could also predispose to spasm in some patients. Similar mechanisms could also be operative in angina precipitated by emotion or cold because coronary vascular resistance increases significantly in patients with coronary disease compared with that of normal subjects during a cold pressor test.[16]

The cause of spasm itself is unknown and may be variable because the coronary circulation is innervated by both parasympathetic and sympathetic nerves, with the epicardial vessels being supplied by alpha and, to a lesser degree, beta adrenergic receptors. In patients with variant angina, Yasue et al.[17] demonstrated that ischemia could be reproduced by methycholine, a parasympathomimetic agent (as did other investigators)[18] or epinephrine, an alpha adrenergic stimulator. Conversely, parasympathetic blockade with atropine or alpha adrenergic blockade with phenoxybenzamine suppressed the ischemic episodes. Ischemia could also be aggravated by the beta blocking agent propranolol, but it did not occur with beta adrenergic stimulation using isoproterenol. (Interestingly, Prinzmetal was able to prevent ischemic episodes using the beta adrenergic stimulator nylidrin.) Thus, the parasympathetic and sympathetic nerves may play important roles in provoking coronary spasm, although the factors that increase coronary reactivity to spasm are unknown.

Uses, limitations and risks of provocative tests: Ergonovine maleate, an ergot alkaloid with a direct constrictive effect on vascular smooth muscle, is the most widely used agent to provoke coronary spasm. Several reports[1,9,19,20] have indicated that in progressive doses of 0.1 to 0.3 mg it is a sensitive, specific and safe means of provoking spasm in patients with variant angina and in some patients with myocardial infarction and normal coronary arteriograms. However, patients without clinical evidence of coronary disease and those with chest pain or angina and normal coronary arteries have not exhibited spasm. This specificity and sensitivity may be dose-related because, when 0.2 to 0.6 mg of ergonovine was given to 15 patients with angina, pain was induced in 14 and S-T depression of 1 mm or more occurred in most.[21]

The absence of demonstrable spasm after administration of ergonovine does not indicate that spasm may not be operative. Ergonovine is a nonspecific vasoconstrictor and the vasospastic stimulus may depend on the type and degree of provocation utilized. Thus, an area of potential spasm that does not respond to a nonspecific vasoconstrictor could respond to an agent acting on the autonomic nervous system. In addition, provoked spasm cannot yet be equated with spontaneous spasm although their characteristics may prove to be similar.[9]

Provocative testing for coronary spasm is associated with potential risk. Ergonovine, in small doses, has been reported to be relatively safe in patients with normal control coronary arteriograms. However, spontaneous episodes of variant angina are frequently associated with severe arrhythmias, and ergonovine has caused ventricular tachycardia, heart block and bradycardia.[1,9,19] Methycholine has also caused complete heart block.[21] In the earlier study of Scherf et al.[22] in which

larger doses of ergot alkaloid were used, one patient died. It may also be that coronary arteriography is not the ideal means of demonstrating spasm. Its demonstration is hindered by the arteriographer's understandable concern about the safety of injecting contrast agent into the coronary circulation during a severe ischemic episode. At catheterization, spasm may be either induced by the catheter or prevented from occuring spontaneously by the vasodilating effect of the angiographic contrast material and premedication. Although spontaneous or provoked spasm causes pain and electrocardiographic changes whereas catheter-induced spasm does not, the relation between the two can at times be confusing. In addition, coronary spasm that is superimposed on a significant fixed obstruction, a relation not adequately studied to date, may be difficult to interpret accurately from an angiogram unless a complete occlusion results. Thus, the electrocardiogram and myocardial imaging might be more sensitive, specific and safer (with appropriate means available for treating complications) methods for identifying coronary spasm.

In summary, it is clear that there is increasing interest in the role of coronary arterial spasm in ischemic heart disease. Although most studies have been focused on variant angina, spasm may also be causally related to other forms of nonexertional angina, acute myocardial infarction and sudden death in at least a subgroup of patients. Provocative testing has become an important means of increasing our understanding of the role of spasm although additional information is required to define the sensitivity, specificity and risk of the vasospastic agents. The diagnosis of coronary spasm clearly has important therapeutic implications. Although it seems clear that bypass surgery is not effective,[20] it is possible that specific drug therapy (perhaps favorably affecting the autonomic nervous system) might be more appropriate than the current use of nonspecific vasodilators such as nitroglycerin[23] or nitroprusside.[24] Certainly, it is conceivable that pharmacologic agents that both provoke and relieve coronary spasm may play an increasingly important role in both our understanding and treatment of patients with various clinical expressions of ischemic heart disease.

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LETTERS TO THE EDITOR

PROPHYLACTIC CORONARY BYPASS SURGERY

I cannot find fault with the conclusions of Selzer and Cohn[1] that (1) the *prophylactic* value of coronary bypass surgery in preventing myocardial infarction and death has not been established, and (2) further investigation of this subject is necessary before prophylactic bypass surgery can become generally accepted.

However, when weighing the risk-benefit ratio of coronary bypass operations, Selzer and Cohn chose an early report from our institutions[2] citing a 6.9 percent early mortality rate (30 days) in patients operated on through December 1972. When using current decision-making logic, I believe one must consider coronary bypass surgical risks as they exist at this time. Early mortality for all cases of isolated coronary artery bypass was 3.5 percent in 1974[3,4] and was 2.2 percent in 1976 (unpublished data). It is important in weighing the relative risks of alternate courses of action that editorialists not place their hand on the balance. Selection of patients with serious coronary occlusive disease for operation continues to be a challenging problem; it will not be facilitated by citing historical data in lieu of current surgical mortality rates.

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REPLY

Although it might have been preferable to cite some of the newer mortality figures from Houston, the study by Dawson et al. (Ref 2 of Hall's letter) reported in our paper represented the sole available complete manuscript. It seems unreasonable to expect the citation of an abstract, from which population selection and data analysis cannot be critically assessed, "unpublished data" or reports from a journal (*Bulletin of the Texas Heart Institute*) unavailable in most centers today. We have little doubt that the operative mortality has improved over the years at the Texas Heart Institute, as it has in most other centers, and appreciate Hall's updating of their results. Nonetheless, there are numerous institutions in the "early phases" of their surgical experience, and these may well be expected to have operative mortality rates between 3.5 and 7 percent, perhaps even higher.

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CARDIAC OUTPUT AND PULMONARY VASCULAR RESISTANCE IN HYPERTENSION

Atkins et al.[1] found a significant correlation between pulmonary vascular resistance and systemic vascular resistance in hypertensive subjects. On that basis they proposed a common mediating factor or factors. Yet their study demonstrated in the same patients an equally significant correlation between pulmonary vascular resistance and cardiac output. The authors chose arbitrarily to label the correlation as pulmonary vascular resistance influencing cardiac output.

In the absence of hypoxemia, hypercarbia, chronic elevation of pulmonary venous resistance or chronic pulmonary volume overload, the single largest determinant of pulmonary vascular resistance in the mature pulmonary vascular bed is cardiac index.[2] Consistent inverse relations between pulmonary vascular resistance and cardiac index through wide swings in cardiac index have been demonstrated in our laboratory and in others. When cardiac index is kept constant, we have found that only changes in blood viscosity exert a significant influence upon pulmonary vascular resistance in both the presence and the absence of neural variables.[3,4]

I suggest that what the authors are viewing as elevations of pulmonary vascular resistance in hypertensive patients is no more complicated than the reaction of a compliant pulmonary vascular bed to modest depression of cardiac output in their patients. The correlations might be much clearer and cleaner had the authors related vascular resistance and cardiac output to body surface area. What I believe to be marginal cardiac indexes in the study group might become apparent as well.

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REPLY

We agree that cardiac output influences pulmonary and peripheral vascular resistance levels. As shown in Tyson's Reference 2, polycythemia causes a reduction in cardiac output and an increase in resistance to maintain a normal pressure in the systemic and pulmonary systems, and anemia causes an increase in cardiac output that lowers the resistance levels; however, it should be noted that the pressures stayed normal. In our patients the pressures were minimally to moderately elevated.

As has been described classically, elevation of systemic pressure can cause a decrease in heart rate and stroke volume, both decreasing cardiac output through baroreceptor mechanisms.[1] Although no baroreceptor mechanism has been described in the pulmonary system, an elevation in the systemic system could depress cardiac output and, since there is a

relation between systemic vascular resistance and pulmonary vascular resistance, there could be an indirect correlation between cardiac output and pulmonary vascular resistance. These interactions are complex and it is difficult to determine the cause and effect relation between cardiac output and pulmonary vascular resistance. If the pulmonary arterial pressures were normal then it would be reasonable to assume that the pulmonary vascular resistance was influenced by cardiac output as Tyson suggests; however, the pressures tend to be high and thus the relation is inappropriate. Whether the relation is direct by either cardiac output or pulmonary vascular resistance affecting the other or whether both are secondary to other factors is not known. Hence we intended just to report the relation without suggesting cause or effect.

Eighteen of our patients had a depressed cardiac index, 63 a normal index and 29 an elevated index. The relation between cardiac index and pulmonary vascular resistance is shown in Table I:

TABLE I

Relation Between Cardiac Index and Pulmonary Vascular Resistance*

Cardiac Index (liters/min)	Pulmonary Vascular Resistance (dynes·sec·cm^{-5})			
	<120	120 to 150	150 to 180	>180
<2.5	2	4	3	9
2.5–3.5	25	14	11	13
>3.5	15	9	2	3

* Data indicate the number of patients in each group.

Although there was a slight increase in the number of patients with increased resistance in the group with a low cardiac index, there were significant numbers of patients in the groups with a normal or high cardiac index with inappropriately elevated resistance levels. These data help to support our thesis that pulmonary vascular resistance is elevated secondary to some other factor; and both the systemic and pulmonary vascular resistance levels may be inappropriately high as a result of the same mechanisms.

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QUINIDINE DEMENTIA

Elderly and middle-aged patients with cardiac arrhythmia commonly are treated with quinidine for long periods. In this age group, dementia is also common, but recent evidence suggests that the chronic use of quinidine can itself produce a dementia.

In the first reported case,[1] a patient had been receiving quinidine since an acute myocardial infarction at age 59. By age 69, a severe confusional state had developed. The results of exhaustive neurologic evaluations were normal except for mild diffuse slowing of the electroencephalogram, and the patient was considered to have senile dementia. However, at age 72, administration of quinidine was discontinued, and she demonstrated a remarkable recovery of mental acuity within 24 hours and over the next several months regained her premorbid intellectual level.

A second patient,[2] a 69 year old physician, had been given quinidine at age 63 because of a cardiac arrhythmia. After 5 years, he manifested a major confusional state with psychotic behavior, paranoid ideation and disorientation for time and place. Neurodiagnostic evaluations in Canada and the United States found no cause for the dementia, and he was considered to have a "toxic psychosis of unknown cause." Treatment with quinidine was continued until the patient's brother, an anesthesiologist, read the first report[1] of quinidine dementia and suggested to the attending physician that quinidine might be the toxin. Upon discontinuation of the quinidine, the patient had a remarkable, rapid and essentially complete recovery "to his witty, original, shrewd (let alone oriented) self."[2]

This second patient was fortunate to have as a family member a physician who read my original article on quinidine dementia. It is important that those most often prescribing quinidine be made aware of the possible relation between its long-term use and the development of a progressive but reversible dementia. Otherwise, elaborate neurologic evaluations may be pursued or, worse, the patient may continue to be given quinidine.

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PROPRANOLOL, P_{50} AND OXYGEN DELIVERY

Note: The opinions or assertations contained herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

Schrumpf et al.[1] observed a rightward shift in the hemoglobin-oxygen equilibrium curve in patients receiving long-term propranolol therapy. To illustrate the significance of this effect the authors calculated that a 3.5 mm Hg increase in the partial pressure of oxygen at which hemoglobin is 50 percent saturated (P_{50}) would produce an increase in oxygen delivery to tissues of 2.1 ml O_2/100 ml of blood flow (a 38.5 percent increase). Their calculations assumed a normal oxygen-carrying capacity of 21 volumes percent and a normal mixed venous PO_2 of 40 mm Hg. However, the absolute change in oxygen delivery resulting from increases in P_{50} is also dependent upon hemoglobin oxygen-carrying capacity. For example, consider the study's first patient whose hemoglobin concentration is 11 g/dl. The oxygen-carrying capacity would be approximately 15.3 volumes percent (11 g/dl × 1.39 ml O_2/g hemoglobin). With the authors' formula, the increase in tissue oxygen delivery in this patient with the same change in P_{50}

would be approximately 1.3 ml O_2/100 ml of blood flow (a 29 percent rather than a 38.5 percent increase). In addition, for any given mixed venous PO_2, the lower the oxygen-carrying capacity of the blood, the smaller is the achievable arteriovenous oxygen difference. As a result of these combined effects, decreases in blood oxygen-carrying capacity tend to offset the benefits of increases in P_{50}.

The mixing technique[2] used by Schrumpf et al. for determination of P_{50} adequately defines the position of the hemoglobin-oxygen equilibrium for a given oxygen tension but does not quantitate the blood's oxygen-carrying capacity. Thus, the study demonstrates an increase in P_{50} with propranolol therapy but does not consider the possibility that the drug might also reduce the maximal volume of oxygen that can be bound to each gram of measurable hemoglobin. This possibility can be excluded by direct measurement of the oxygen content of an aliquot of fully oxygenated blood.

The conclusion that P_{50} increased during propranolol therapy seems valid. However, any consideration of changes in oxygen delivery resulting from increases in P_{50} should include the effect of possible changes in oxygen-carrying capacity. The argument that propranolol may enhance systemic oxygen delivery would have been strengthened by demonstrating that the drug does not alter the blood's oxygen-carrying capacity.

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REPLY

Humphrey and Alter have made a valid point that the oxygen carrying capacity of the blood is a critical determinant of oxygen delivery to tissues. However, our study demonstrated no change in either hemoglobin or hematocrit consequent to propranolol administration. To turn their conclusion around, it has not been demonstrated that propranolol *does* alter the blood's oxygen-carrying capacity.

In any event, as concluded in our report, the precise increase in oxygen delivery produced by propranolol cannot really be calculated. The change would be different at the usual low PO_2 of coronary sinus blood compared with the peripheral vein blood analyzed in our study. There is a gradient of PO_2 from subepicardium to subendocardium, and coronary atherosclerosis itself is a heterogenous disease. Therefore, we concluded that "at any tissue PO_2 level, there would be some increase in oxygen unloading. . . . the measurable effects of such a shift would be difficult to predict."

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WRAPPING OF AORTIC ANEURYSM

Kolff et al.[1] present a method of handling aneurysm of the aortic arch. The technique consists of wrapping the dilated arch with Dacron graft, a method described by us in January 1971[2] and successfully applied by us in more than 80 patients. Sorry to say, this fact was entirely disregarded by the authors. Figure 1 shows, at top, an illustration from our 1976 article[3] and, at bottom, Figure 3 of the article by Kolff et al.

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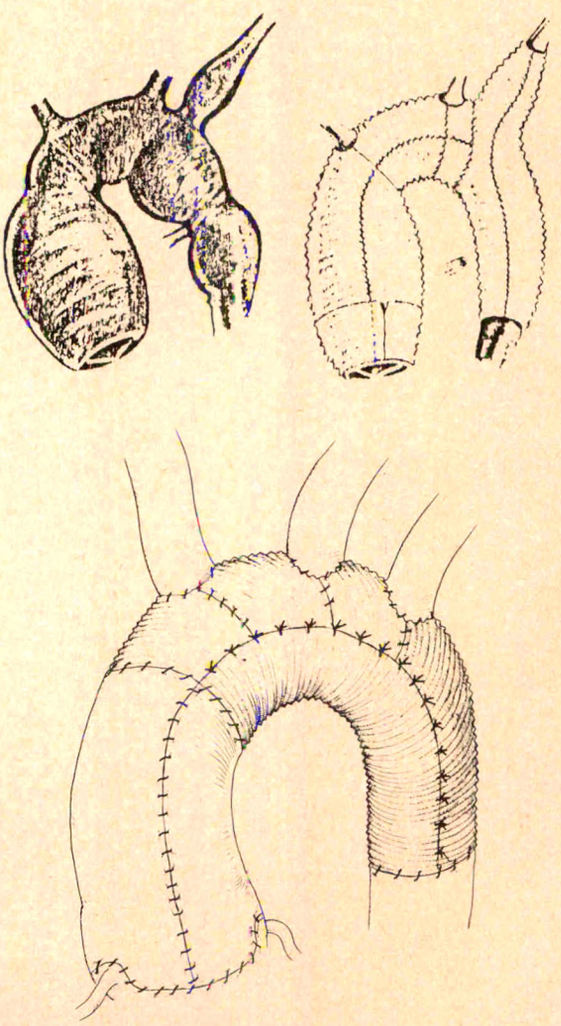


FIGURE 1. Top, illustration of method of wrapping dilated aortic arch as reported by Robicsek et al. in 1976[3] (reprinted by permission). **Bottom,** illustration from article by Kolff et al.[1]

REPLY

We thank Robicsek for pointing out our omission of the fact that for atherosclerotic aneurysms wrapping has been successfully used by him and reported in the past. Although the drawing submitted is from a 1976 article and the method was applied in other than aortic dissections, we appreciate his pointing out that wrapping of aneurysms in general has had a long history.

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HEART RATE AFTER ATROPINE

In the letter by Duvernoy et al.,[1] Figure 1 (resting electrocardiogram showing a typical pattern of Wolff-Parkinson-White syndrome, type B) appears to be mislabeled. Before atropine the heart rate is high; after atropine it is low. There is no explanation for this peculiar phenomenon.

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Reference

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REPLY

The resting heart rate in Figure 1 is approximately 60 beats/min, and is again 55 to 60 beats/min in the lower strip, obviously obtained before atropine was given. After atropine the rate increased mildly to about 83 beats/min. Atropine was given in an attempt to normalize atrioventricular conduction, and the two strips were mislabeled.

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REDUCTION OF SUDDEN DEATH BY AORTOCORONARY BYPASS SURGERY—I

Vismara et al.[1] raise some very important questions, not only about the efficacy of coronary bypass surgery, but also about the appropriate methodology for evaluating therapeutic results. They assert that coronary arterial surgery reduces the incidence of sudden death due to ischemic heart disease. If this conclusion is supportable, the impact is momentous, for that places us squarely on the threshold of prophylactic coronary bypass surgery. The Davis group has made so many outstanding contributions to cardiology that we believe it essential to point out what might be deficiencies in the study lest it be accepted on their authority without critical analysis. We believe that the conclusions of the authors are not justified because of errors of methodology and statistical analysis.

The major source of difficulty and potential error is the basic design of the study with respect to equality of the surgical and medical treatment groups. The investigators acknowledge that comparison of groups is valid only if the groups are equal, and they affirm that in their study, "the proper circumstances pertained that allowed coronary patients with similar anatomic disease and symptoms to be equally matched for maximal surgical versus medical therapy . . . ." Our concern is over "the proper circumstances" and what actually did pertain.

To make a valid comparison, the study and control groups must be the same or nearly the same by all important criteria.[2] The best methods known must be marshalled to produce data that can be interpreted with scientific assurance of their accuracy. Although there may be limitations in our knowledge, at present the minimal requirements for scientific determination of equal treatment and control groups include, among other things, the following methodologic principles (for objective end points): (1) prospective study; (2) randomization; (3) criteria for inclusion and exclusion; (4) defined end points; (5) appropriate statistical analysis.[3] It is meaningful to apply these principles to the study under question.

Unless a study is prospective, with experimental design preceding therapeutic intervention, it is impossible to incorporate the safeguards necessary for a valid comparison of the study and control groups. Was the Davis study indeed prospective; that is, was it planned in advance to be as described in the final paper? The importance of a prospective study is in setting the rules before, not after, completion of the study, primarily to prevent manipulation of the data. In this study the criteria for inclusion or exclusion from the study were formulated at the completion of data gathering, thus nullifying any advantages of prospective planning. As the authors note, "The clinical evaluation at the time of angiography established that the surgical and medical groups were comparable . . . ." In view of their surgical selection process, this could be done only *after* collection of all the data, demonstrating in fact that there was no prospective design to ensure equal groups, but rather a retrospective determination of such. It is not enough to legitimize a study by calling it prospective; the design must be so as well. This study appears not to have been prospective in any meaningful manner.

Randomization is the best method of assuring unbiased selection of patients for a treatment under study.[4–6] True randomization of treatment allocation eliminates the investigator from any element of choice and is achieved by a defined mathematical process.[7] Randomization is also the best method of balancing treatment groups with respect to prognostic variables. The real question in this and other nonrandomized studies is whether the treatment and control groups can be created equal in the absence of randomization. All available evidence is that this is not practically possible.[2] In any case, after the fact adjustments are not a satisfactory substitute for proper randomization. To create equal groups by deliberate selection, as in this study, the investigators must act without bias in allocating patients to the study or the control group, and they also must be aware of all prognostic factors that could influence the outcome of the study. The second problem is impossible to deal with completely because the most unbiased investigator may be unaware of certain prognostic factors that may be represented more in one group than in another. As noted in their report, patients in this study were *selected* for either surgical or nonsurgical treatment on the basis of what the clinicians thought was best for each individual patient. Although there was an attempt to match certain prognostic

variables primarily reflecting left ventricular function, other known and unknown prognostic variables, such as propensity for life-threatening arrhythmias, were not matched. Furthermore, selection of "matched" groups assumes that we know and can match all factors of prognostic importance; this is an unjustified assumption. Analysis of the Davis study will show a normal and natural bias that operated in patient selection. Without randomization of patients to treatment and control groups, as in the Davis study, it is almost impossible to avoid important differences between the groups, as we will demonstrate later.

Criteria for inclusion and exclusion of patients into a study should be set before initiation of the study, and then adhered to for the remainder of the study. Tampering with these criteria, although perhaps giving the appearance of equalizing the groups, affords the inevitable opportunity to introduce bias (unwittingly) in patient selection. For instance, 17 surgically treated patients with a ventricular filling pressure of less than 7 mm Hg were excluded from the Davis study, for the given reason that all medically treated patients had a ventricular filling pressure exceeding that level. Did this exclusion equalize the groups? It may appear so, but what if these 17 patients had other important prognostic characteristics that would have altered the results one way or the other? Is it not possible that these 17 patients had a worse prognosis than 17 other surgically treated patients included in the study? Regardless, after the fact exclusions always involve the possibility of introducing bias into selection of groups, and such exclusions should not be allowed if "proper circumstances" are to prevail.

A further unjustified exclusion is that of the five patients who died at operation. These patients certainly died suddenly and unexpectedly. If medically treated patients died of causes related to drugs (medical treatment), were those deaths excluded? Why should one form of sudden death be excluded, when others are not? Was the end point clearly and fairly defined? There is usually no disagreement concerning the presence or absence of death, but when sudden death is defined as ". . . death occurring within 6 hours [Why 6? Was this decided prospectively or retrospectively?] of symptoms, clinically attributable to unexpected arrhythmias, and unrelated to congestive heart failure, shock or systemic illness," there is a great deal of room for subjective difference of opinion. Who determines what is an acceptable symptom, or whether the patient had congestive failure? An investigator with a strong bias for or against the specific treatment under study could easily influence the results by his interpretations of "sudden death." In such a case, an impartial noninvestigator, blinded to the treatment of the patient, should judge the presence or absence of sudden death.

Although statistical analysis in itself does not endow a study with objectivity or validity, it is an important component of proper investigational design. Statistical analysis has two important components: the analysis itself and, more important, a determination of whether the data deserve to be analyzed. Analysis of the Davis data reveals that the treatment and control groups are not demonstrably equal despite a contrary claim. The basic error is in statistical analysis. In establishing that treatment and control groups are *equal*, it is not valid to apply a statistical test that is used to establish the probability that there is no *difference* between groups. Equality is not the same as absence of a statistically significant difference. Statistical comparisons between samples (groups) are based on the null hypothesis, which states that there is no difference between two things. Deciding not to reject the null hypothesis because there is a greater than 5 percent probability ($P > 0.05$) that the difference between the samples could have resulted from sampling error is not the same as accepting the null hypothesis that there is no difference between the groups.

TABLE I
Preoperative Indexes of Left Ventricular Function: Comparison of Surgical and Medical Groups*

	Chi-square (*corrected*)	*P* Value	Probability that the Difference is Due to Sampling Error and not Due to a Difference Between Groups
Left ventricular contractile pattern	3.11	0.08	8%
Akinesia or dyskinesia	3.16	0.08	8%
Two or more segments of akinesia or dyskinesia	1.16	0.28	28%
Diffuse left ventricular dysfunction	2.51	0.11	11%

* Data taken from study of Vismara et al.[1]

For example, analysis of the Davis data on patients with either akinesia or dyskinesia by the chi square test shows that the *P* value is 0.08. This means that there is only an 8 percent chance that the difference between the groups (for this variable) is due to sampling error. Put another way, there is only an 8 percent chance that the difference in the data is due to sampling error and not to an inherent difference between the groups. To be satisfied that sampling error is not the cause of a *difference* between samples we arbitrarily require a less than 5 percent chance of sampling error. To establish that two samples are the *same* it is not acceptable to simply show that $P > 0.05$. In looking at four variables of left ventricular function (Table I), there is a clear difference between the surgical and medical groups. The differences between these groups are not statistically significant at a *P* value of < 0.05, but there are important differences, and it is not valid to say that the groups are equal. Indeed, our analysis indicates a probability that the groups were in fact different with respect to left ventricular function.

Chi square analysis of the presence of angina in the two groups before treatment shows a statistically significant difference ($P < 0.05$), with more angina in the surgical group. The statement[1] that the *P* value is > 0.05 is in error, if we use the reported results of angina occurring in 83 percent of the medical patients and in 95 percent of the surgical patients.

Critical review of this very important report thus indicates that the surgical and medical groups were so selected that surgically treated patients had more angina but better myocardial function than the medically treated patients. This is not surprising because the natural bias of most cardiologists is to offer surgical therapy to the patients with the most symptoms but the least risk. Previous studies,[9–11] initially presumed to have evenly matched treatment and control groups, have had this same inherent bias of selection. There is no evidence that the study design was truly prospective in terms of patient selection or controls: Allocation of patients was not randomized; after the fact exclusions were allowed,

the end point was not wholly objective and the statistical analysis was not appropriate. From these observations we conclude that the treatment and control groups were not equal, and thus the data are not worthy of analysis.

The conclusion of the authors that successful coronary bypass surgery enhances life expectancy may or may not prove to be true in the long run, but their study is without scientific validity with regard to this conclusion. At a time when proper scientific studies are possible, we believe it is improper to report conclusions based on inadequately designed studies because such conclusions may be wrong and misleading.[5,12]

To conclude that this study is not valid is not proof that it is wrong; it says only that we have no scientific proof that coronary arterial surgery produces the benefit claimed. The primary challenge is to infuse scientific methodology into medical investigation so that results and conclusions are acceptable. Perhaps the greatest contribution of science is that it provides the means by which we can restrain ourselves from reaching conclusions that may later on prove to be incorrect. The cause of coronary surgery would be better served by suppressing the desire to publish data that may not hold up to rigorous examination and by insisting on scientific validation of therapies before their widespread application.

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REDUCTION OF SUDDEN DEATH BY AORTOCORONARY BYPASS SURGERY—II

Vismara et al. compared the incidence of sudden death in 121 patients with coronary artery disease who had vein bypass graft surgery with the incidence in 96 patients treated medically. The incidence of sudden death in the surgical group was 7 of 121 (5.8 percent) compared with 23 of 96 (24 percent) in the medical group with a P value of <0.001. The authors conclude that coronary bypass surgery was responsible for the lesser incidence of sudden death in the surgical group. Several aspects of their analysis suggest that factors other than surgery were responsible for the difference.

1. The authors chose to eliminate five patients who died during surgery. In a comparison of two treatment methods the mortality of the therapy should be included in the overall mortality. Because operative deaths usually occur in high risk patients who would be highly prone to sudden death if not operated on, this biases the statistics in favor of surgery. Were five similar patients removed from the medical group?

2. The authors excluded from the surgical group an unknown number of patients who had mitral valve replacement or aneurysmectomy. How many were excluded and how many deaths occurred in this group? The reader should be favored with this information because this is a high risk group. If such patients were removed from the surgical group, why were similar patients not removed from the medical group? The exclusions from the surgical group are difficult to evaluate. Originally 172 patients were in the group. Exclusions from the surgical group were 5 patients who died at operation, 5 patients with congestive heart failure, 4 patients who died of noncardiac causes and 17 patients with low left ventricular end-diastolic pressure. This leaves 31 patients not accounted for. Were these the patients who had aneurysmectomy or valve replacement?

3. The paper does not give any data regarding how many medical patients subsequently had surgery. This is always a problem in the follow-up evaluation of the results of medical therapy. Were such patients eliminated entirely from the medical group? This is suggested by the authors' statement that "... all patients remained throughout the study period within the therapeutic group (surgical versus medical) to which they were initially assigned."

4. Were ejection fractions similar in both groups? No data are given on this point despite increasing evidence that the ejection fraction is one of the most important risk factors determining mortality in coronary disease.

5. Despite the attempt to achieve two groups at similar risk, several unfavorable risk factors were more prevalent in the medical group, including (a) an abnormal pattern of left ventricular contraction (71 percent surgical group, 82 percent medical group), and (b) diffuse left ventricular dysfunction (3 percent surgical group, 9 percent medical group).

6. Sudden death is not defined.

7. The manipulation of statistics employed in this paper gives the reader considerable difficulty in evaluating the results and may raise doubt regarding the authors' conclusions. A more unbiased presentation would evaluate the comparative data without the exclusions the authors chose to make so that the reader could compare the results.

8. The total mortality rate in the medical group is very high (38 percent in 39 months). In the Veterans Administration Cooperative Study the 3 year mortality rate in the medical group was 16 percent and in the high risk medical group 23 percent.

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REPLY

We appreciate the intense interest of Preston and Spodick and of Hultgren concerning the efficacy of elective coronary bypass

grafting in general and particularly in regard to our recent article on improved longevity due to reduction of sudden death by such surgery. Their letters represent the two principal viewpoints of those reluctant to consider seriously the validity of circumstantial evidence about coronary bypass surgery and longevity: (1) essential requirement of perfect design (Preston-Spodick), and (2) invaluable nature of multicenter trials (Hultgren). Because the first is unachievable practically and the second possesses inherent problems of design, the influence of coronary surgery on survival will be largely judged properly by those willing to formulate flexible decisions based on evaluation of the growing body of literature pertaining to the effect of such surgery on life span.

We emphasize that our data, as carefully pointed out in our study, represent a portion of this growing body of literature providing circumstantial evidence that elective coronary bypass, carried out in certain medical centers in properly selected subgroups of coronary patients with chronic stable angina pectoris, more effectively reduces angina and extends longevity than currently available medical therapy. Thus, our study in itself neither claims nor is intended to be definitive, thereby allaying the initial fears of the critics. In a disorder as complex as chronic ischemic heart disease, global conclusions from a single study on bypass surgery are not warranted by either enthusiasts or antagonists.[1] Nevertheless, we consider that our investigation, in conjunction with the favorable reports of many others,[2–21] affords unique and valuable insight. We believe that it will contribute toward the eventual substantiation of the view that elective coronary bypass surgery, relative to medical treatment including propranolol, improves survival by reducing the incidence of sudden death in specific subsets of patients with chronic stable angina who are at high risk of dying from ischemic heart disease because of advanced coronary arteriosclerosis and who are suitable candidates for the operative procedure.

Response to Preston and Spodick: The fundamental assumption that widespread application of coronary bypass surgery is economically prohibitive compared with medical care for coronary disease should not go unchallenged.[22,23] In fact, preliminary objective evidence that the reverse is actually the case has already been provided in work from the Peter Bent Brigham Hospital.[24] We are in accord with the majority of the idealistic statements of Preston and Spodick concerning what criteria constitute a perfectly designed study of the merits of coronary bypass surgery. However, we are not in agreement that it is not possible to obtain important and meaningful truths from somewhat less than ideal circumstances, provided that appropriate compensation is incorporated in the study design. We are certain that Preston and Spodick do not mean to imply that all investigations not precisely fulfilling every aspect of each of their listed platitudes are incapable of contributing valid information.

Preston and Spodick are incorrect in assuming that our "criteria for inclusion or exclusion from the study were formulated at the completion of data gathering" and that "there was no prospective design to ensure equal groups." In contrast, our rules that "all patients were categorized in a standardized fashion with regard to cardiac symptoms, coronary risk factors, left ventricular function and angiographically documented coronary pathoanatomy" were established before acquisition and analysis of data, as indicated in the Methods section and specifically addressed in the second paragraph of our Discussion. Further, we clearly specify that, after having decided upon these variables for assessment, these factors were examined and then prospective long-term evaluation of prognosis was carried out for more than 3 years in both the medically and surgically treated groups.

Although randomization is generally considered the best means for unbiased selection, this principle may have serious drawbacks when applied to multicenter trials in which it is not possible to isolate the subject under investigation (in this case, efficacy of surgery) as the single independent variable. There is genuine concern that potential effectiveness of coronary bypass surgery in a participating center or by a surgeon particularly adept in the procedure may become obscured by dilution[25] even among a consortium of leading medical centers with a large volume of cases. Although treatment was not randomized in our study, as our report readily acknowledged, this possible restriction was compensated for by meticulous comparison of the aforementioned factors known to affect prognosis in coronary disease. As we carefully delineated, both the medical and surgical groups comprised patients with similar broad ranges of untoward clinical manifestations, atherogenic precursors, ventricular dysfunction and multivessel obstruction. That 17 surgical patients with normal cardiac performance were excluded actually strengthened our comparison of the two groups; moreover, each of these 17 patients survived with a dramatic reduction of angina pectoris. If one wants to delve into the problems of so-called after the fact exclusions, such examples are readily apparent in the Veterans Administration cooperative study of treatment of chronic stable angina.[26]

Because a principal question analyzed in our study was the follow-up incidence of sudden death in surgically and medically treated patients, our long-term 3 year evaluation excluded the five patients who died at operation. Importantly, even inclusion of these five patients as cases of surgical sudden death did not alter the statistical significance of the difference between the data concerning longevity and manner of death in the medical and surgical groups. To clear their confusion about drug therapy during the follow-up period we refer Preston and Spodick to paragraph 6 of our Results section; it clearly states that such treatment was similar in both groups with the exception that more medical patients required propranolol, and neither overall mortality nor mode of mortality was statistically influenced by drug therapy in the two groups. Relative to the critics' remarks about how sudden death was ascertained, they are referred to the final paragraph of the Methods section and the final paragraph of the Results section. These paragraphs clearly state that all deaths were witnessed and that the majority were instantaneous.

Although Preston and Spodick may debate the value of statistics, such evaluation is necessary in the assessment of scientific data, and we applied appropriate methodology in defining statistical significance. Table I of Preston and Spodick's letter reinforces the accuracy of our statistics (paragraph 2, Results) on the similarity of preoperative segmental ventricular dyssynergy of the two groups. Concerning the presence of angina before treatment, there was no statistical difference between the two groups, as we clearly indicated (paragraph 1, Results). Although we recognize that the absence of statistical significance may not necessarily indicate total lack of physiologic difference, Preston and Spodick fail to comment on whether their analysis favors the medical or surgical group. The remainder of the Preston-Spodick letter reiterates what has been verbosely said previously and adds some purely emotional speculation. At this point, because we have carefully explained our position in our article and in this communication, we ask the reader to use his good judgment in formulating his own considered conclusions. Parenthetically, we wish that Preston and Spodick had devoted themselves with equal vigor to such analysis of the Veterans Administration cooperative study of treatment of chronic stable angina[26]; disappointingly, the antithesis was the case.[27]

Response to Hultgren: Statistical significance was still achieved by counting the five operative deaths as surgical sudden deaths in relation to (1) the superiority of coronary bypass surgery over medical therapy in reducing overall mortality, and (2) the lowered mortality rate thereby observed with surgery as a result of a diminished incidence of sudden death. Concerning the number of patients in the medical and surgical groups and those excluded from each, it is important to remember that our study evaluated matched patients that were not randomized. Thus, although each group had approximately 100 patients (96 medical group versus 121 surgical group), the precise number of patients constituting each group is substantially less important than the fundamental factor that the two groups were essentially the same before treatment in regard to prevalence and degree of the following: symptoms (angina and cardiac decompensation), coronary risk factors, left ventricular dysfunction (defined at cardiac catheterization) and extent of multivessel obstruction documented with coronary arteriography. To maintain such equality of cardiac performance before treatment for the subsequent long-term follow-up assessment of symptomatic relief, longevity and manner of cardiac death, surgically treated patients requiring mitral valve replacement or aneurysmectomy and, similarly, all medically treated patients with papillary muscle dysfunction or ventricular aneurysms were excluded from the long-term evaluation period (as stated in paragraph 1, Methods and paragraph 4, Results). In regard to the query about the surgically treated patients apparently not accounted for, these 20 (not 31) patients did indeed constitute those who underwent valve replacement or aneurysmectomy (or had recent myocardial infarction, prior cardiac surgery or serious noncardiovascular systemic illness) (paragraph 1, Methods).

In contrast to one of the principal deficiencies of the Veterans Administration cooperative study of treatment of chronic stable angina,[26] *none* of our 96 medically treated patients subsequently underwent coronary bypass surgery or were lost to follow-up during the 3 year period of prospective long-term evaluation. Thus our statement in paragraph 2 of the Methods section means precisely what it says: "All patients remained throughout the study period within the therapeutic group (surgical versus medical) to which they were initially assigned." The interpretation that this sentence implies that some of our medical patients were nonadherers is absolutely incorrect.

Ventricular function did not differ statistically in the medical and surgical groups. This pertains to cardiac output, left ventricular end-diastolic pressure and extent and nature of abnormal left ventricular contraction pattern (paragraph 2, Results) as well as to ejection fraction. For the definition of sudden death, the critic is referred to the last paragraphs of the Methods and Results sections: Sudden death was always witnessed, occurred within 6 hours of onset of symptoms and was instantaneous in the majority of instances.

Finally, the Hultgren letter terminates on most tenuous ground by contending that the mortality rate appears high in our medically treated patients in comparison with that of the medically treated group in the Veteran Administration cooperative study.[26] To begin with, Hultgren misrepresents the cardiac mortality rate of our medical group and describes a fictitious total mortality rate of 38 percent in 39 months. In contrast, as stated throughout our paper and discussed in depth in paragraph 4 of the Discussion section, the overall cardiac mortality rate for our medical group was 10 percent per year. Because all of our medically treated patients (as well as our surgically treated patients) had two or three major vessel obstruction, the prognosis of our medically treated patients is quite consistent with previously reported data. The annual mortality rate of medically treated patients with angina pectoris and multivessel stenosis has been established to range from 7 to 13 percent for two vessel disease and from 10 to 16 percent for three vessel disease.[28,29] Furthermore, because more than two thirds of our medically treated patients manifested triple vessel coronary obstruction, our annual death rate was within the lower range for medical therapy alone. Thus it is evident that the more favorable prognosis achieved by coronary bypass grafting in our surgical patients with multivessel disease (mortality rate only 5 percent per year including the initial operative deaths), was not the result of excessive mortality in the medical group.

In regard to the 3 year mortality rate of 16 percent in the medical group claimed in the Veterans Administration cooperative study,[26] the serious flaws in comparing this spuriously low death rate to patients with multivessel coronary disease is perhaps already common knowledge.[30] Thereby, only a few of the inequities need to be pointed out: the medical mortality rate of the Veterans Administration cooperative study was concocted by excluding medical nonadherers (the major being treatment failures),[31] eliminating patients with left main coronary obstruction, including patients with single coronary vessel stenosis, and so forth.[26]

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Presidents' Page

Cardiology: Present Status and Future Direction



Leonard S. Dreifus, MD, FACC

The following is the acceptance speech given by Dr. Dreifus at the 27th Annual Scientific Sessions of the American College of Cardiology, March 8, 1978, Anaheim, California.

It is with great honor and pleasure that I accept the Presidency of the American College of Cardiology for 1978 to 1979. I am deeply indebted to those members of the College and my immediate predecessor, Dr. Dean Mason, who have contributed so much to the development and progress of the College. The growth of this organization can largely be attributed to those who had the great foresight and imagination to work for our ideals and carry these ideals to fruition. My position of responsibility and leadership comes at a most unsettled time in American medicine.

Your College has recently mandated precise goals and objectives. These goals embrace the important mission for developing programs of high quality in continuing education related to the learning needs of professionals who care for patients with cardiovascular disease. Furthermore, the College has pledged to originate and utilize methods for teaching and learning. Heart House now stands as a monument to the future structure of education and research. It will meet the learner's specific needs so that the delivery of health care in cardiovascular diseases will profit enormously in the future. I have had the opportunity to direct two courses at Heart House, which has been a most gratifying experience. All of us are enthusiastic to create course material for this new innovation in learning. I hope all of you will be able to participate in this new endeavor.

The College is deeply committed to upgrading training programs, monitoring the requirements and directions for certification, to maintaining high levels of social consciousness and to furthering the organizational structure of the College itself. Most importantly, the College is dedicated to take an active role in cooperation with other organizations and agencies to maintain continuing high standards for delivery of quality cardiovascular health care. The College is keenly aware and stands ready to honor its ever emerging role as a principal source of advice to government agencies and other organizations concerning all aspects of cardiovascular health care. It is to this latter objective that I would like to spend a few moments with you.

It gives me no great delight to state that never has American medicine been so effective in containing disease and yet, paradoxically, it is under critical fire from private as well as government sectors. The contributions of physicians to the community are essential to its very survival. The physician is the central decision maker for more than 70 percent of health care services totalling more than $160 billion per year. It has been generally recognized that when the cost of health care begins to approach 10 percent of the gross national product, society will reject any further expenditures. I might add that the bureaucracy alone manages to dispose of more than 47 percent of our gross national product.

The press has reported that more than $4 billion are spent on unnecessary surgery each year in this country. Consequently, it is no small surprise that the controversies over saphenous bypass graft surgery, at a cost in excess of $1 billion, are now under critical review. Happily, the mortality rate due to cardiovascular disease has decreased more than 30 percent since 1950. This decrease is now continuing at 6 percent per year. The present scientific program, with its new investigative data, papers and symposia, attest to the importance of these issues now facing the public and College alike. Regrettably, when the public is unsure where to turn for redress, it begins to listen to politicians who promise to set everything right with rules and regulations.

Through our Government Relations Committee, headed by Dr. Charles Fisch, we have been asked to develop guidelines for the budgetary requirements of cardiovascular needs in this country. Our Bethesda Conferences have been the primary source in reviewing and developing recommendations for cardiac pharmacology, critical care, manpower, standards of health care and cardiovascular examination for aircrew certification of the Federal Aviation Administration. We are dedicated to review the measures necessary for prevention of morbidity and mortality due to coronary heart disease and to offer recommendations for the more efficient delivery of critical cardiac care in the community. The College, through its committees, continues to ensure that the various agencies of the government do not dilute or misdirect the intent of our legislative bodies contrary to the needs and interests of patients. I believe that the past record of the College and its expert and well reasoned testimony will impart a strong influence on future legislation. Heretofore, our rec-

ommendations have played a major role to increase funding for the renewal legislation of National Heart, Lung, and Blood Institute training programs. I am assured we will continue to render effective consultation in the future development of federal health legislation. We cannot ascribe to arbitrary cost reduction at the expense of quality and accessibility of health care. I am dedicated to the concept that will assure continued high quality and equal access to medical care, and I will resist any and all measures that would deny patients equal protection of their health under the law.

In the year ahead we can look to further involvement of the College in all of these very important issues. The problems are complex and the answers do not come easily. You have opportunities to make your thoughts known through your various Governors and committee chairmen. It is my fondest hope that this will be a year of great progress.

Leonard S. Dreifus, MD, FACC received his premedical education at the University of Pennsylvania and his medical education at Hahnemann Medical College. After interning at the Philadelphia General Hospital, he served as a medical resident there. He was a trainee of the National Institutes of Health from 1954 to 1956 and a Fellow in Cardiovascular Research at the Michael Reese Hospital in Chicago during the same period. He served as Chief of Cardiology at the United States Army Hospital in Valley Forge from 1956 to 1958, and was Director of the Electrophysiologic Units at Hahnemann Medical College from 1960 to 1974. At present he is Professor of Medicine at the Jefferson Medical College of the Thomas Jefferson University, and Chief of the Cardiovascular Department at the Lankenau Hospital.

Dr. Dreifus is a member of the AOA; Consultant to the Division of Professional and Technical Development, Department of Health, Education and Welfare, and is Special Consultant to the Social Security Administration of the Department of Health, Education, and Welfare. He was president of the Southeastern Pennsylvania Chapter of the American Heart Association from 1975 to 1976, and serves on their Board of Governors. He was President of the Philadelphia Physiological Society from 1970 to 1971 and is on the Board of Trustees of the Alumni Association of Hahnemann Medical College.

He is active in the American College of Cardiology, serving as Secretary from 1969 to 1970, Vice President from 1973 to 1974, and from 1976 to 1977, and President Elect from 1977 to 1978. He is also on the Board of Trustees. He was Chairman of the 8th Bethesda Conference in 1975 and Chairman of the Bethesda Conference Committee from 1975 to 1977. He received the Master Teacher Award from the College in 1972.

He received the Cummings Award in 1975 for the State Department Teaching Mission to Iran, Greece and Belgium. He was the David Fleet duPont Memorial Lecturer in 1976 at the Delaware Academy of Medicine, and the Jack Lesser Memorial Lecturer in 1976 at the Deborah Heart and Lung Center. In 1977 he was the Truitt Lecturer at the University of Texas in Houston.

Dr. Dreifus has published more than 150 original scientific contributions and is the author of 4 textbooks. He is on the Editorial Boards of the American Journal of Cardiology, American Heart Journal, Coeur et Medecine Intern (Paris), Heart and Lung, European Journal of Cardiology *and* Clinical Cardiology.

28th ANNUAL SCIENTIFIC SESSION
AMERICAN COLLEGE OF CARDIOLOGY.

MARCH 11–15, 1979 MIAMI BEACH, FLORIDA

CALENDAR OF EXTRAMURAL PROGRAMS

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Extramural Programs Department, Division of Continuing Education, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

APRIL 1978 THROUGH AUGUST 1978

To be arranged individually **Preceptorships in Cardiology.** Arthur Selzer, FACC, director, Pacific Medical Center, San Francisco, CA

APR. 3–7 **Consultant's Course in Cardiology.** Michael V. Herman, FACC, director and Simon Dack, FACC, Richard Gorlin, FACC and Louis E. Teicholz, FACC, co-directors. Mount Sinai Medical Center, New York, NY

APR. 3–12 **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC and James E. Crockett, FACC, directors. Rancho Santa Fe Inn, Rancho Santa Fe, CA

APR. 12–14 **vectorcardiograpny: A Basic Workshop.** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, AZ

APR. 19–21 **Echocardiographic Solutions to Clinical Cardiovascular Problems.** Joseph K. Perloff, FACC and John S. Child, FACC, directors. Century Plaza Hotel, Los Angeles, CA

MAY 8–11 **The Physiologic Basis for Diagnosis and Treatment of the Patient With Heart Disease—A Tribute to William Harvey on his 400th Birthday (1578–1657).** J. Willis Hurst, FACC, director and Robert C. Schlant, FACC, co-director. Colony Square Hotel, Atlanta, GA

MAY 12–14 **Rational Drug Therapy in Ischemic Heart Disease.** Robert J. Lee, director, Palmer House, Chicago, IL

MAY 12–15 **A Symposium on Cardiovascular Nursing.** Henry J. L. Marriott, FACC and Leo Schamroth, FACC, directors. Sheraton Sand Key Hotel, Clearwater Beach, FL

MAY 18–20 **Cardiovascular Nuclear Medicine and Comparative Techniques: 1978.** Lawrence S. Cohen, FACC, Alexander Gottschalk, Barry L. Zaret, FACC, directors. Yale University School of Medicine, New Haven, CT

JUNE 15–17 **Echocardiography: Fundamentals and New Developments in Cardiac Ultrasound.** Arthur D. Hagan, FACC, director and Walter V. R. Vieweg, FACC and Joel S. Karliner, FACC, co-directors. Sheraton Harbor Island Hotel, San Diego, CA

Aug. 26–28 **Tutorials in the Tetons: Cardiac Emergencies (Fourth Annual).** Robert S. Eliot, FACC, director and Alan D. Forker, FACC, William P. Nelson, FACC and Gerald L. Wolf, co-directors. Jackson Lake Lodge, Moran, WY

LEARNING CENTER: PROGRAM CALENDAR

The American College of Cardiology's newest department, the Learning Center, located at the College's Bethesda, Maryland headquarters, began operations last October with the offering of its first continuing medical education program for physicians with a specialty or an interest in cardiovascular medicine. The purpose of the Learning Center is to support the professional commitment to quality patient care by providing a new standard of excellence in cardiovascular continuing education.

Each continuing education program is directed toward a specific target group including: adult cardiologists (CD), internists (IM), pediatric cardiologists (PDC), and family practitioners (FP). For additional information concerning the programs listed below or for a complete schedule of programs through October 1978, contact Program Coordinator, Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014 (301) 897-5400.

APRIL THROUGH JUNE 1978

Apr. 3–6 **Cardiac Emergencies: Recognition and Therapy (CD) (IM).** Charles E. Rackley, MD, FACC, director

Apr. 10–12 & 13–15 **Adult Echocardiography: Clinical Applications and Recent Advances (CD) (IM).** Pravin M. Shah, MD, FACC, director

Apr. 17–20 **Pediatric Echocardiography (PDC).** Richard A. Meyer, MD, FACC, director

Apr. 24–26 **Exercise Testing: Diagnostic and Physiologic Considerations (CD) (IM).** Keith Cohn, MD, FACC, director

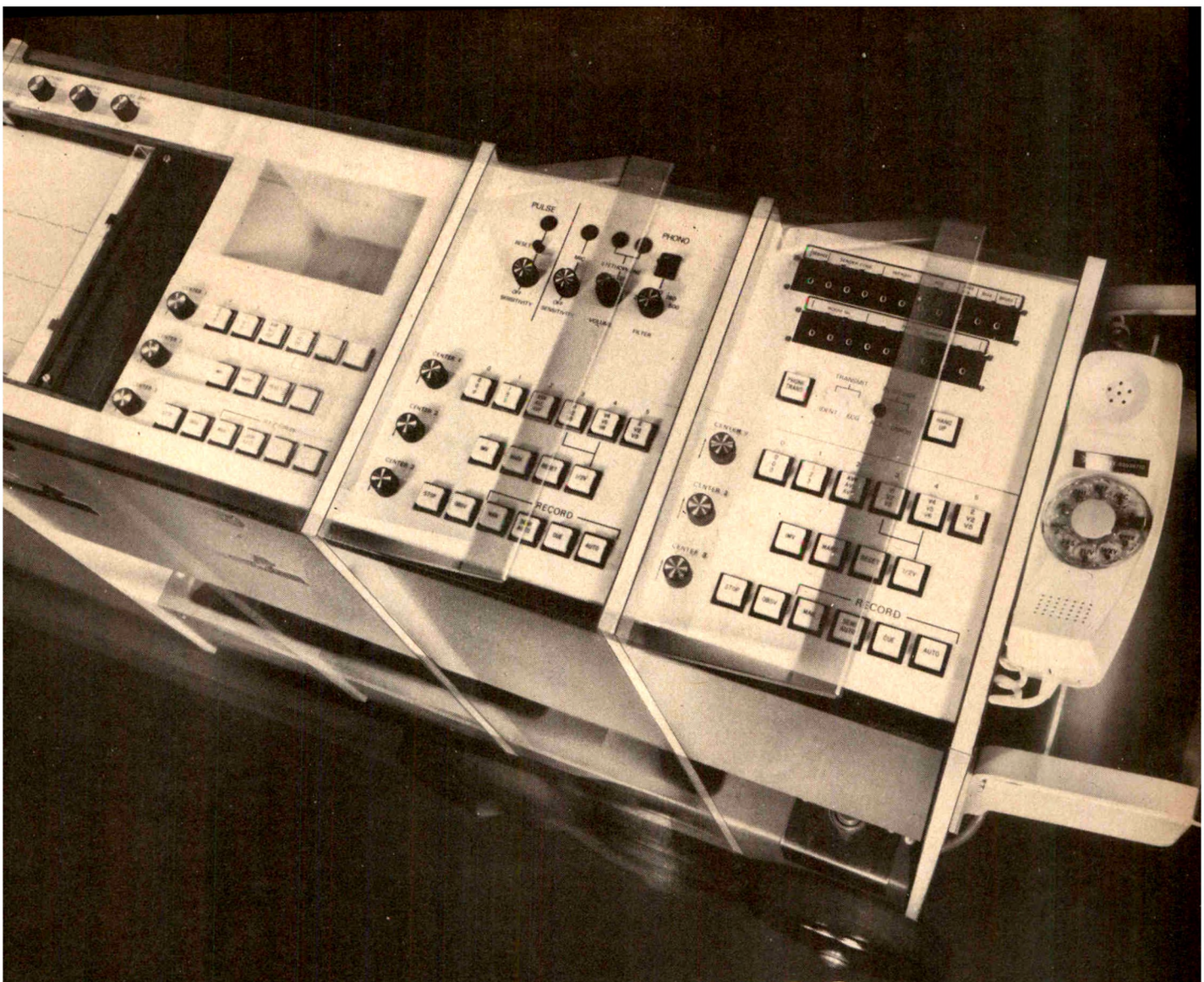
May 8–10 & 22–24 **Electrocardiography of Arrhythmias (CD) (IM).** Charles Fisch, MD, FACC, director

May 15–18 **Update in Cardiology (CD).** R. Joe Noble, MD, FACC, director

May 31–June 2 **Diagnosis & Management of Clinically Important Arrhythmias (FP) (GP) (IM).** William P. Nelson, MD, FACC, director

June 19–22 **Congestive Heart Failure: A Changing Scene (CD) (IM).** Charles B. Mullins, MD, FACC, director

June 12–14 & October 23–25 **Update in Cardiology (CD) (IM).** Douglas P. Zipes, MD, FACC



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Or perhaps you see it as a way to eliminate the costly duplication of a dedicated stress test system. For unmatched flexibility, you can team it with your choice of two types of monitors, three different treadmills and either manual treadmill controls or automatic test control. When the full modular system's not in use, just disconnect the 3038/2 for stand-alone ECG use and get the best of both worlds.

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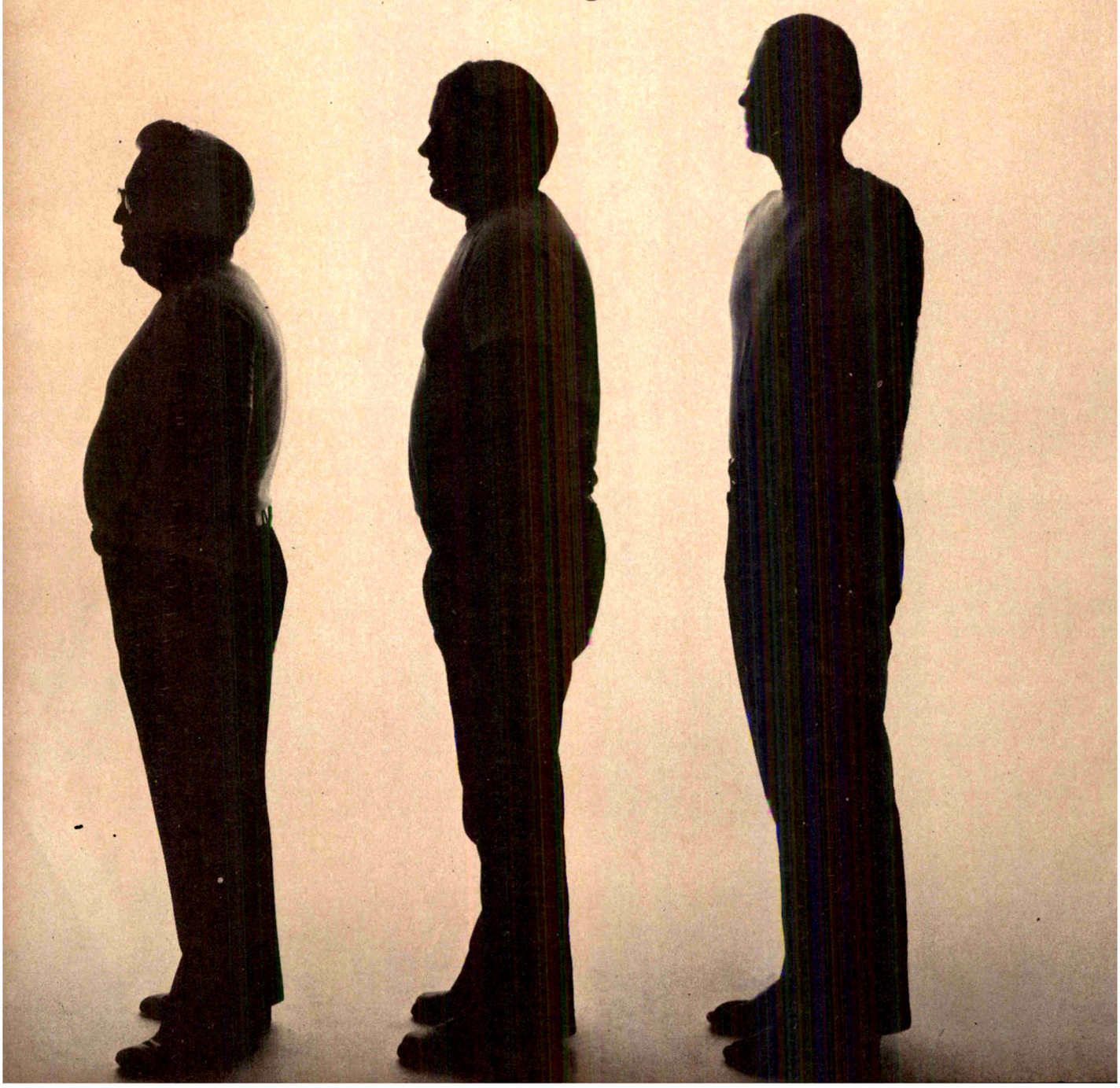
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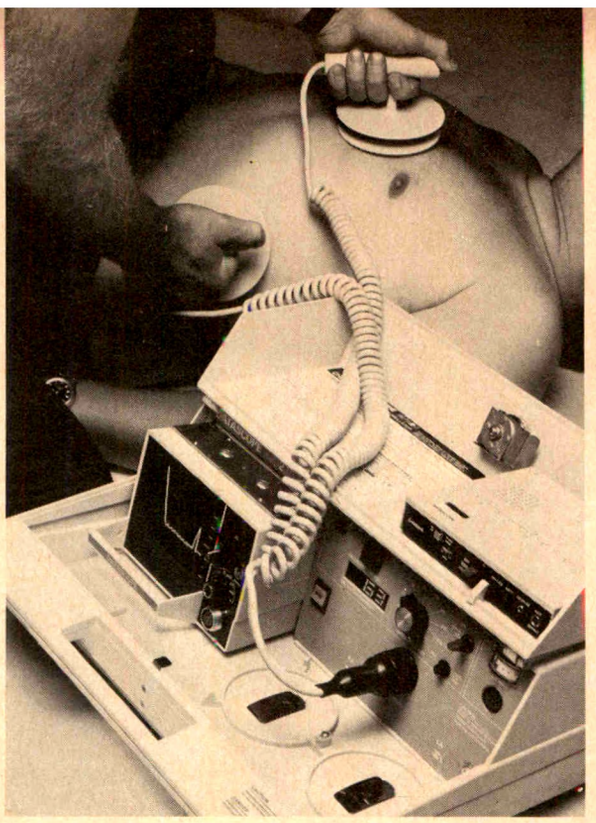
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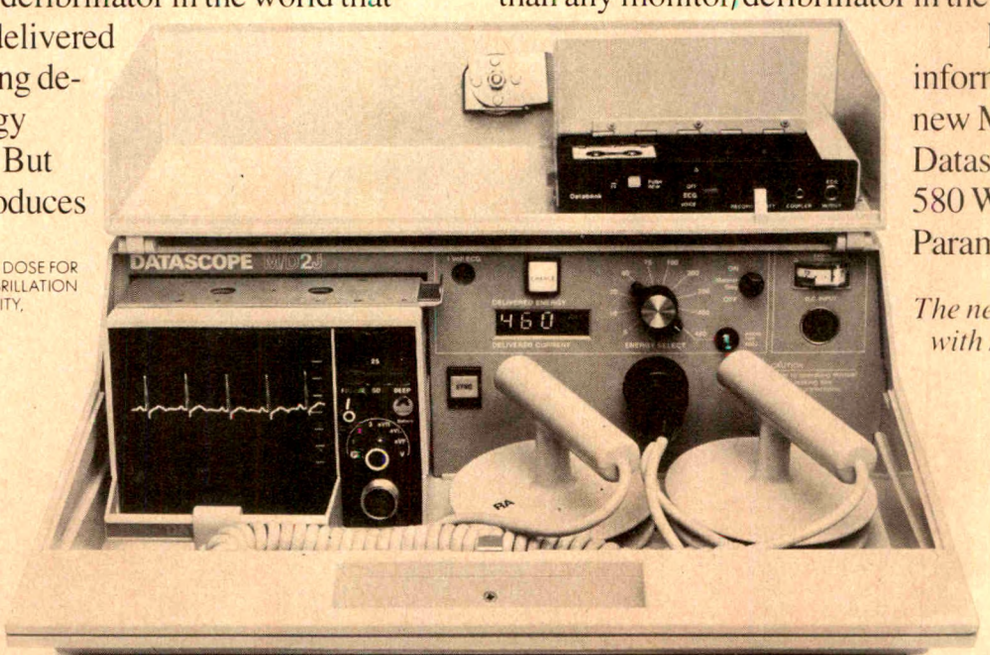
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*CKER, JR., W.A.: ELECTRICAL DOSE FOR FIBRILLATION. CARDIAC DEFIBRILLATION CONFERENCE, PURDUE UNIVERSITY, P. 121-7, OCT. '75.

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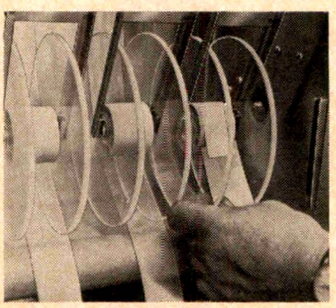
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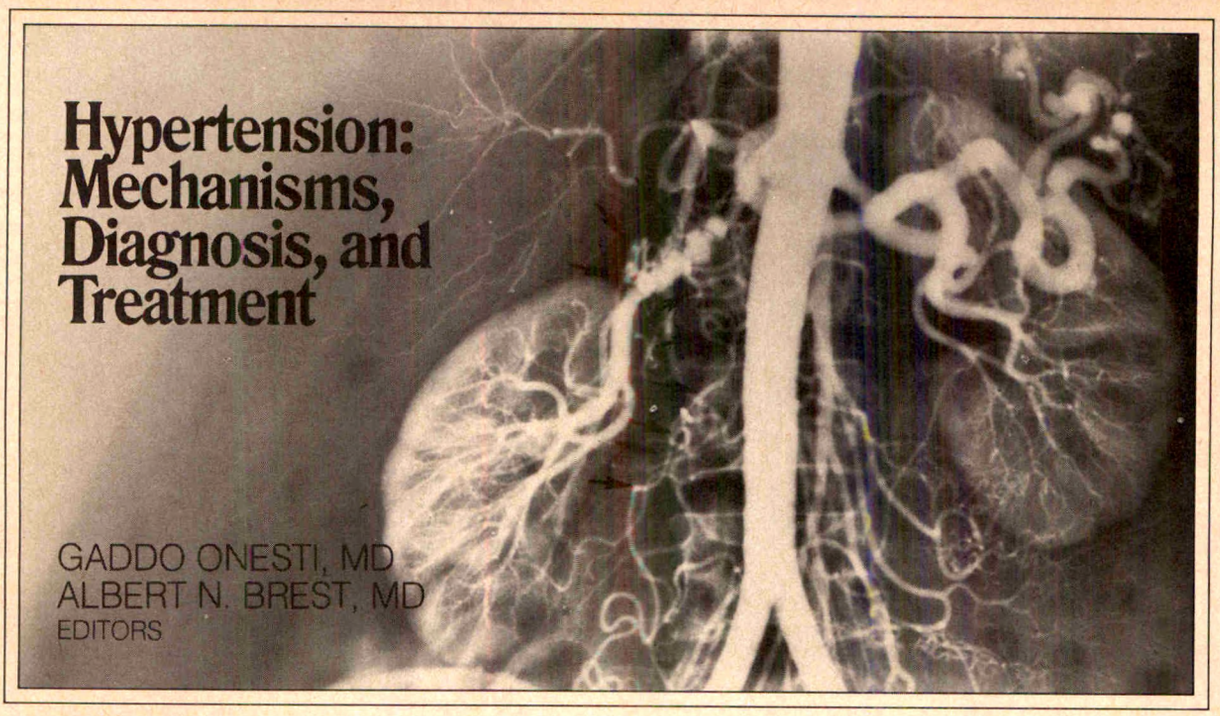
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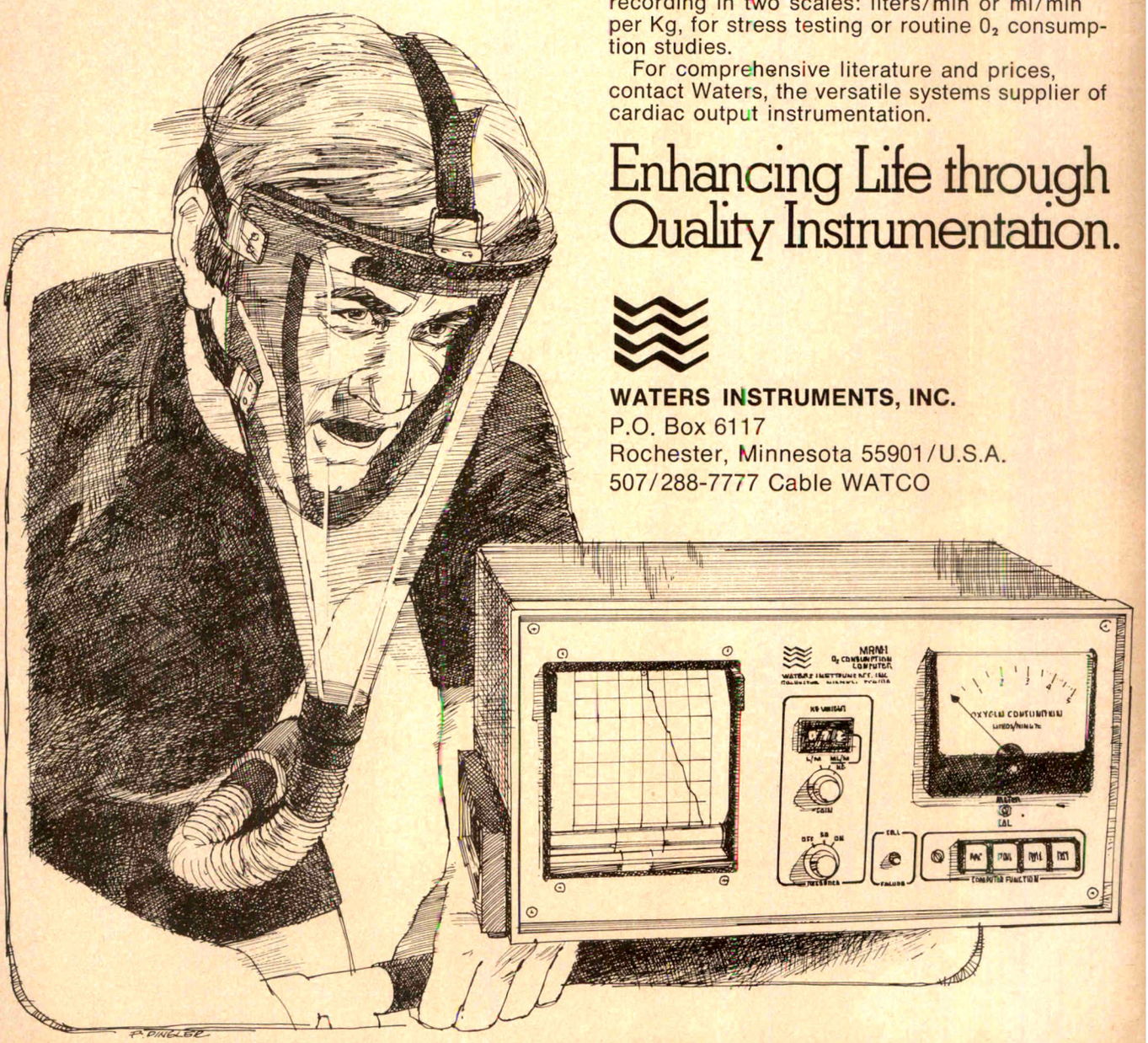
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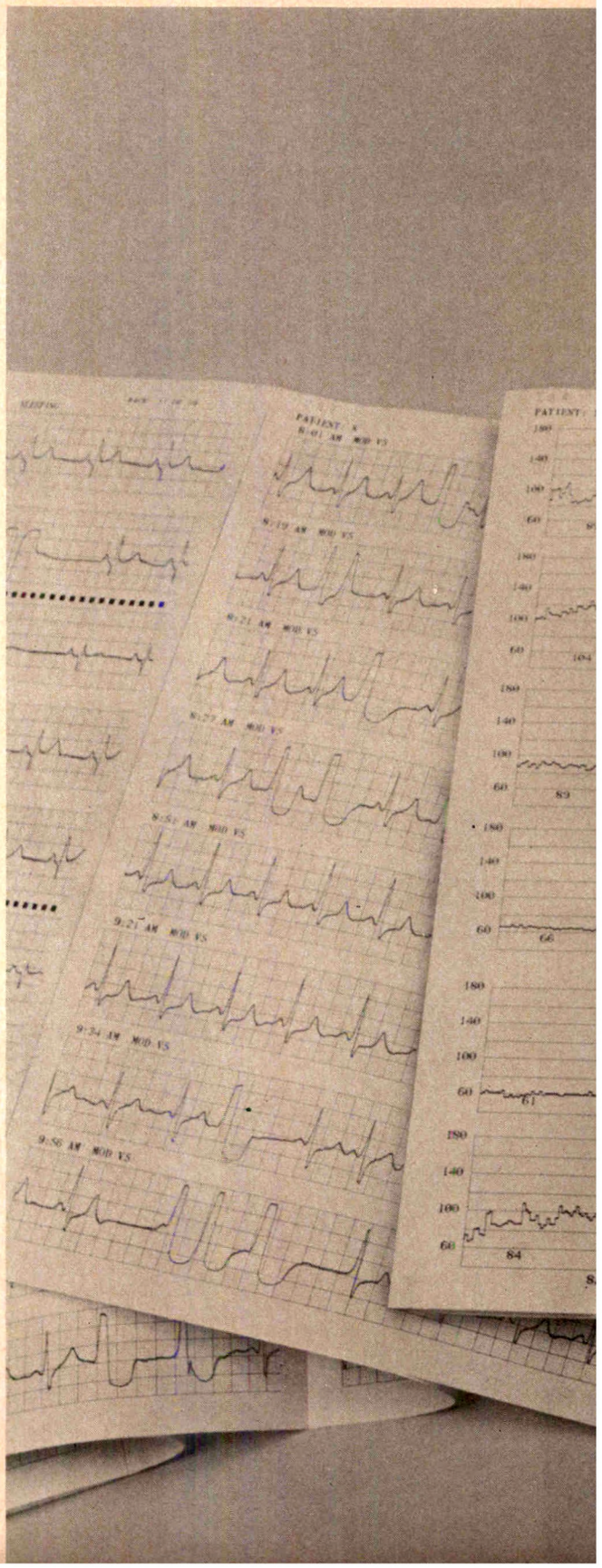
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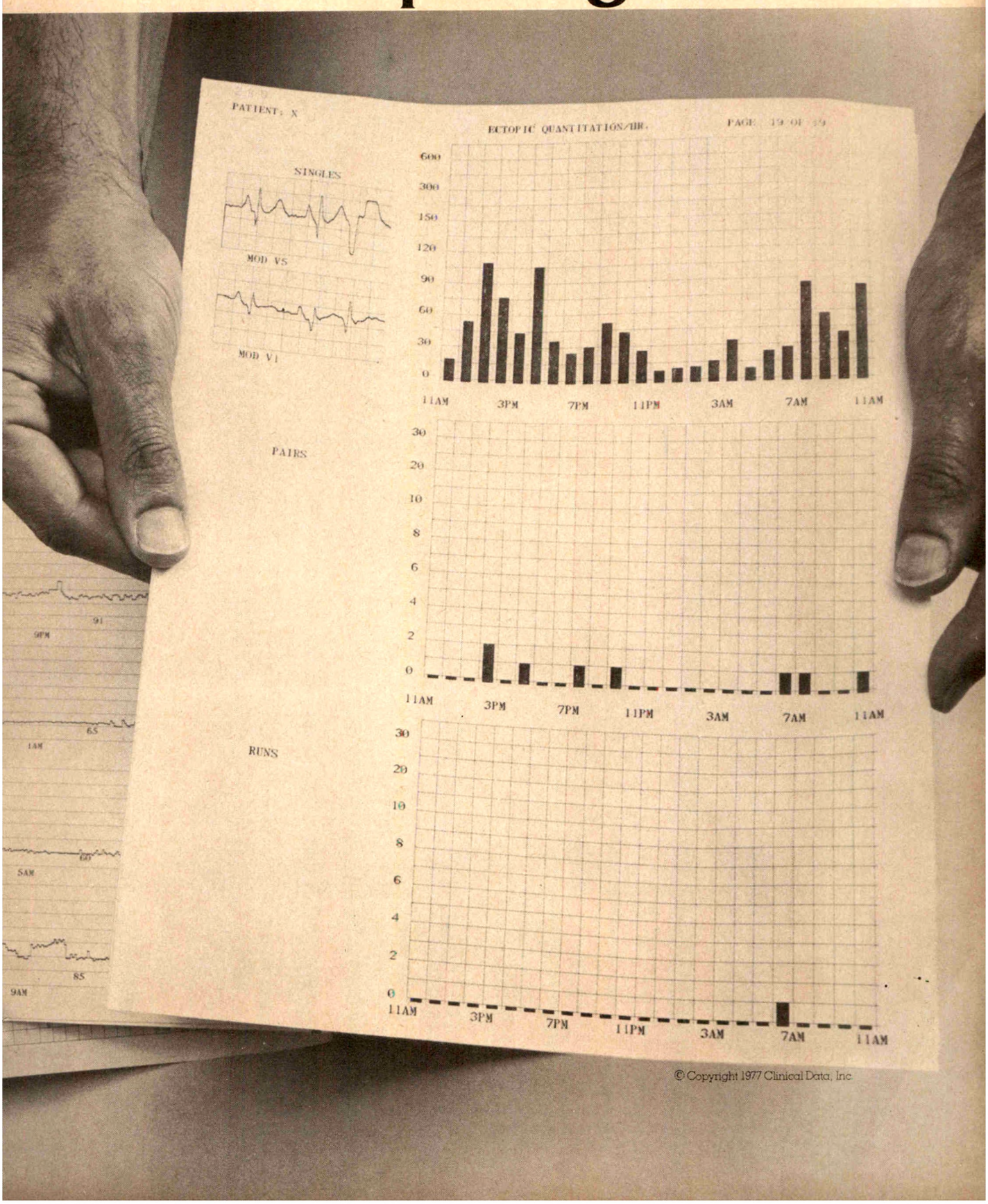
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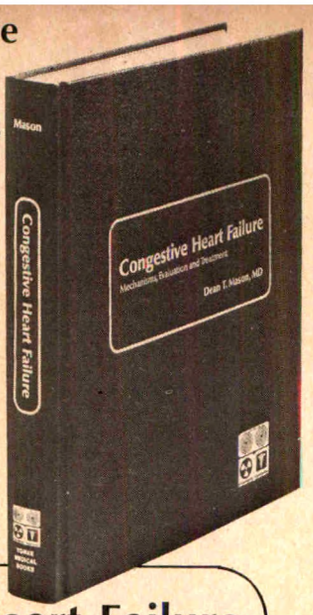
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About the author . . . Dean T. Mason, M.D.

Professor of Medicine, Professor Physiology, Chief of Cardiovascular Medicine, University of California, School of Medicine, Davis.

President, American College of Cardiology; President, Western Society for Clinical Research.

Member of the American Board of Internal Medicine Cardiovascular Diseases.

Has authored more than 400 original articles on cardiovascular science and clinical cardiology.

Serves on the editorial boards of The American Journal of Cardiology, The Journal of Clinical Investigation, Circulation, Chest, Clinical Pharmacology and Therapeutics, Catheterization and Cardiovascular Diagnosis, and Heart and Lung.

Recipient of Experimental Therapeutics Award in 1973 from the American Society of Pharmacology and Experimental Therapeutics, the Research Awards in 1965 from the American Therapeutic Society, and the Theodore and Susan B. Cummings Humanitarian Awards in 1972, 1973, and 1975 from the U.S. State Department and the American College of Cardiology.

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A110

SEARLE

Aldactazide®

(spironolactone 25 mg./
hydrochlorothiazide 25 mg.)

WARNING

Spironolactone, an ingredient of Aldactazide, has been shown to be a tumorigen in chronic toxicity studies in rats (see *Warnings*). Aldactazide should be used only in those conditions described under *Indications*. Unnecessary use of this drug should be avoided.

Fixed-dose combination drugs are not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Indications: Cirrhosis of the liver accompanied by edema and/or ascites. Essential hypertension, edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate.

Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, hyperkalemia or acute or severe hepatic failure. Allergy to thiazide diuretics or to other sulfonamide-derived drugs.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactazide. Do not administer concurrently with other potassium-sparing diuretics. Sulfonamide derivatives including thiazides have been reported to exacerbate or activate systemic lupus erythematosus.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75 and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hypokalemia may develop as a result of profound diuresis, particularly when Aldactazide is used concomitantly with loop diuretics, glucocorticoids or ACTH. Transient elevation of BUN may occur. Dilutional hyponatremia or rarely low-salt syndrome may develop. Gynecomastia may develop and in rare instances some breast enlargement may persist.

Thiazides may alter the metabolism of uric acid and carbohydrates with possible hyperuricemia, gout and decreased glucose tolerance. Vascular responsiveness to norepinephrine is reduced. Thiazides may also increase the responsiveness to tubocurarine. Thiazides may decrease serum PBI levels and prolonged therapy may induce hypercalcemia and hypophosphatemia.

Spironolactone may and hydrochlorothiazide does cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. Breast feeding should be discontinued when Aldactazide is being used.

Adverse Reactions:

Associated with spironolactone: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established.

Associated with thiazides: Gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhea, abdominal cramps), purpura, thrombocytopenia, leukopenia, agranulocytosis, dermatologic symptoms (cutaneous eruptions, pruritus, erythema multiforme), paresthesia, acute pancreatitis, jaundice, dizziness, vertigo, headache, xanthopsia, photosensitivity, necrotizing angiitis, aplastic anemia, orthostatic hypotension, muscle spasm, weakness and restlessness.

Adverse reactions are usually reversible upon discontinuation of Aldactazide.

Dosage and Administration

Edema in adults: The usual maintenance dose is one tablet four times daily but may range from one to eight tablets daily depending on the response to the initial titration.

Edema in children: The usual daily maintenance dose should be that which provides 0.75 to 1.5 mg. of spironolactone per pound of body weight (1.65 to 3.3 mg./kg.).

Essential hypertension: Usually two to four tablets daily depending on results of the titration of the individual ingredients.

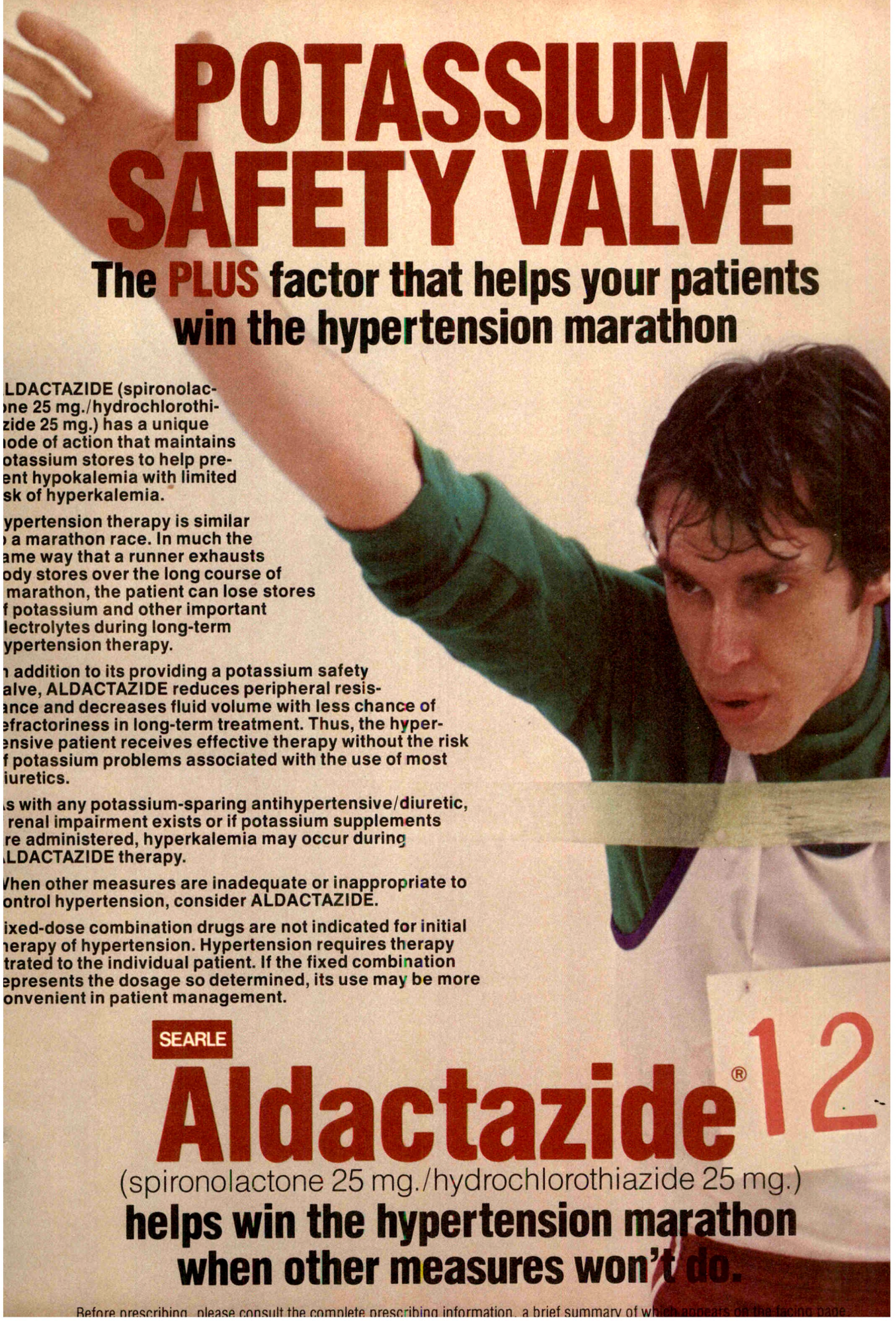
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POTASSIUM SAFETY VALVE

The PLUS factor that helps your patients win the hypertension marathon



LDACTAZIDE (spironolac-
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zide 25 mg.) has a unique
mode of action that maintains
otassium stores to help pre-
ent hypokalemia with limited
sk of hyperkalemia.

ypertension therapy is similar
a marathon race. In much the
ame way that a runner exhausts
ody stores over the long course of
marathon, the patient can lose stores
f potassium and other important
lectrolytes during long-term
ypertension therapy.

n addition to its providing a potassium safety
alve, ALDACTAZIDE reduces peripheral resis-
ance and decreases fluid volume with less chance of
efractoriness in long-term treatment. Thus, the hyper-
ensive patient receives effective therapy without the risk
f potassium problems associated with the use of most
iuretics.

s with any potassium-sparing antihypertensive/diuretic,
renal impairment exists or if potassium supplements
re administered, hyperkalemia may occur during
LDACTAZIDE therapy.

When other measures are inadequate or inappropriate to
ontrol hypertension, consider ALDACTAZIDE.

ixed-dose combination drugs are not indicated for initial
herapy of hypertension. Hypertension requires therapy
trated to the individual patient. If the fixed combination
epresents the dosage so determined, its use may be more
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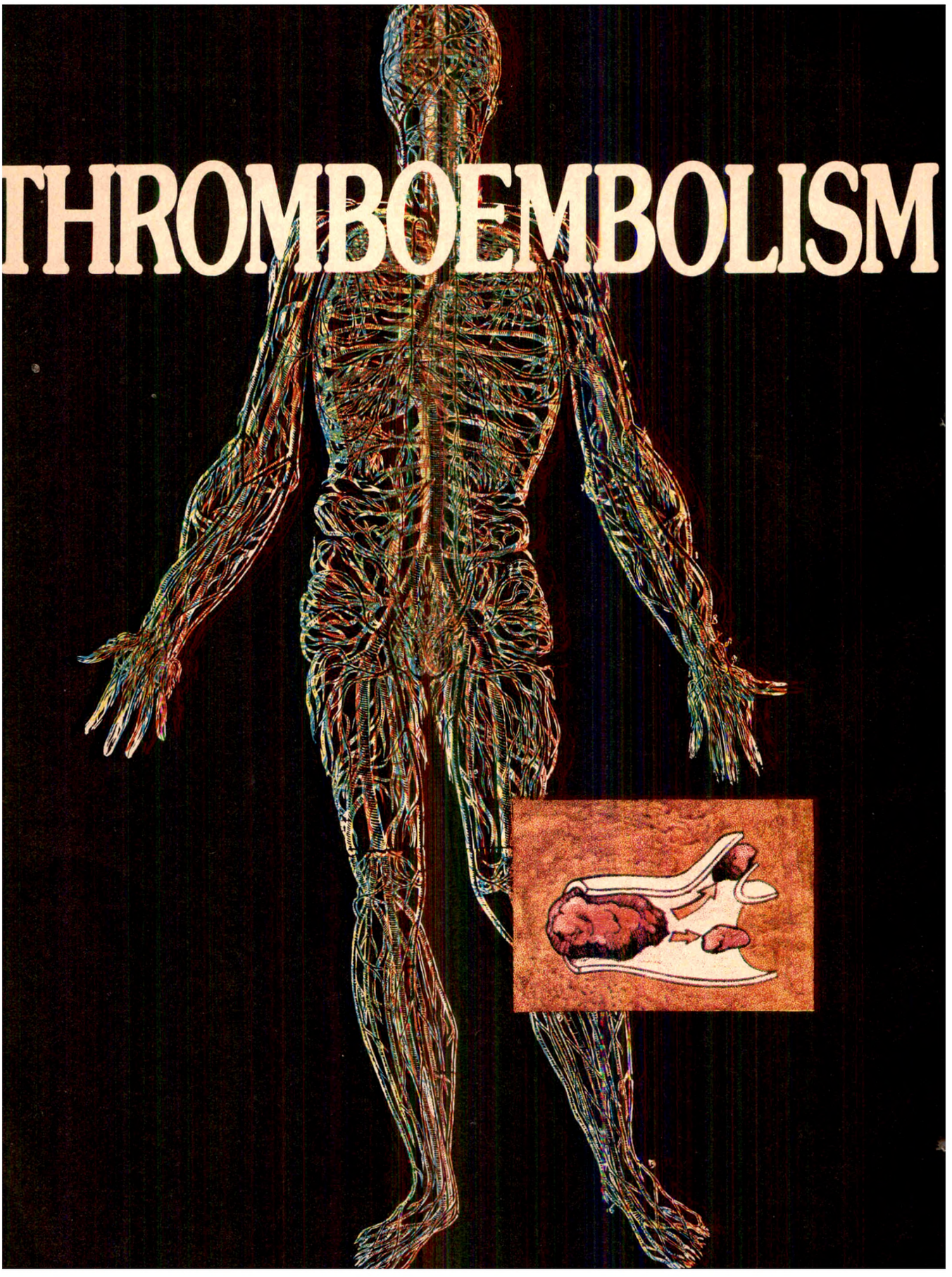
Aldactazide® 12

(spironolactone 25 mg./hydrochlorothiazide 25 mg.)

helps win the hypertension marathon when other measures won't do.

Before prescribing, please consult the complete prescribing information, a brief summary of which appears on the facing page.

THROMBOEMBOLISM



COUMADIN® (CRYSTALLINE SODIUM WARFARIN U.S.P.)

FOR ORAL ANTICOAGULATION

Prophylactic Use

A number of cardiac syndromes can predispose patients to thromboembolic episodes. The greatest threat of thromboembolism, however, exists in patients with a history of obesity, excessive cigarette smoking or previous episodes of venous thrombosis or pulmonary embolism. Postoperative patients requiring extended immobilization and the elderly are at high thromboembolic risk as are the severely injured—particularly those over 40 years with fractures of the hip, pelvis or lower extremities—and patients undergoing elective cup arthroplasty or pelvic surgery.

Emphasis should be placed on prophylaxis for those patients predisposed to thromboembolism. The oral anticoagulant of choice is COUMADIN® (crystalline sodium warfarin U.S.P.)

Therapeutic Use

For established thromboembolism, administration of I.V. heparin followed by oral anticoagulant therapy is a cornerstone of treatment. COUMADIN,® a chemically pure oral anticoagulant with high predictability of response, is a mainstay of effective therapy.

Dosage and Administration

In patients receiving COUMADIN,® prothrombin time should be maintained at 1.5 to 2.5 times the control until results stabilize. Dosage and administration should be individualized according to prothrombin time results and reevaluated periodically throughout therapy.

Patients should be well informed about their condition and medication, since factors such as dietary change, travel, other medication, change in physical condition and abrupt environmental change may influence prothrombin time and, therefore, response to COUMADIN.®

The oral anticoagulant of choice COUMADIN®

(CRYSTALLINE SODIUM WARFARIN U.S.P.)

Endo Laboratories, Inc.
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

DUPONT

Before prescribing, please see prescribing information on following page.

COUMADIN® is an Endo registered U.S. trademark;
U.S. Pat. No. 3,077,481 (Reissue No. 25,866)

COUMADIN®

(CRYSTALLINE SODIUM WARFARIN*)

DESCRIPTION COUMADIN® (crystalline sodium warfarin), a prothrombinopenic anticoagulant, is chemically crystalline sodium warfarin isopropanol clathrate. The crystallization of sodium warfarin virtually eliminates trace impurities present in amorphous sodium warfarin, thus achieving a crystalline product of the highest purity. Warfarin* is the coined generic name for 3-(α-Acetonylbenzyl)-4-hydroxycoumarin. On a dose-for-dose basis, COUMADIN® (crystalline sodium warfarin) is therapeutically equivalent to amorphous sodium warfarin.

ACTIONS COUMADIN® and other coumarin anticoagulants act by depressing synthesis in the liver of several factors which are known to be active in the coagulation mechanisms in a variety of diseases characterized by thromboembolic phenomena. The resultant **in vivo** effect is a sequential depression of Factors VII, IX, X and II. The degree of depression is dependent upon the dosage administered. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombosis has occurred, anticoagulant treatment aims to prevent further extension of the formed clot and prevents secondary thromboembolic complications which may result in serious and possible fatal sequelae.

After oral administration, absorption is essentially complete, and maximal plasma concentrations are reached in 1 to 9 hours. Approximately 97% is bound to albumin within the plasma. COUMADIN® usually induces hypoprothrombinemia in 36 to 72 hours, and its duration of action may persist for 4 to 5 days, thus producing a smooth, long lasting response curve. Little is known of the metabolic pathways involved in the biotransformation of oral anticoagulants in man. However, their metabolites appear to be eliminated principally in the urine.

INDICATIONS Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN® is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Pregnancy—COUMADIN® (crystalline sodium warfarin) is contraindicated in pregnancy because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy. Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms–cerebral, dissecting aorta; (4) pericarditis and pericardial effusions; (5) subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis; or lack of patient cooperation. **Spinal puncture** and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding. **Miscellaneous:** polyarthritis, vitamin C deficiency, major regional, lumbar block anesthesia and malignant hypertension.

WARNINGS Sodium warfarin is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN® are given together, a period of 4 to 5 hours should elapse after the last intravenous dose and 12 to 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when sodium warfarin is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:
Lactation–coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Prolonged dietary deficiency** (cachexia, vitamin K). **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**–sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, menometrorrhagia, allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN®, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN®.

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma, collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders–infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency–steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cinchophen; clofibrate; COUMADIN® overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methyldopa; methylphenidate; metronidazole; monoamine oxidase inhibitors; nalidixic acid; oxolinic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates; sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; trimethoprim/sulfamethoxazole; unreliable prothrombin time determinations.

†Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN® underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN®. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN® (crystalline sodium warfarin) include:

1. Minor or major hemorrhage from any tissue or organ–which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and an extremely rare reaction consisting of hemorrhagic infarction and necrosis of the skin.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN® patient aids are available to physicians on request.

The administration and dosage of COUMADIN® must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K dependent Factors VII, X and II. These factors, in addition to Factor IX, are affected by coumarin* anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN® should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic prothrombinopenia are 1½ to 2½ times the normal prothrombin time (e.g. 21 to 35 seconds, with a control of 14 seconds).

Induction–40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Maintenance–Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy–The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery–The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN® be adjusted to maintain the prothrombin time at approximately 1½ to 2 times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN® with Heparin–Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in situations of great emergency to administer sodium heparin initially along with COUMADIN®. The initial dose of heparin and injectable COUMADIN® may be administered together in the same syringe. It should be noted that heparin may affect the prothrombin time, and therefore, when patients are receiving both heparin and COUMADIN®, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, and preferably 4 to 5 hours after the last intravenous injection or 12 to 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN® (crystalline sodium warfarin), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN® may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN® administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can be obtained.

SUPPLIED Tablets: COUMADIN® (crystalline sodium warfarin). For oral use, single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white, 25 mg red. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100.

Injection: Available as single injection units of amorphous sodium warfarin lyophilized for intravenous or intramuscular use in a box of 6 units for use immediately after reconstitution. 50 mg: Unit consists of 1 vial, 50 mg; sodium chloride, 10 mg; thimerosal, 0.2 mg, pH is adjusted with sodium hydroxide; accompanied by a 2 ml ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

*Present as crystalline sodium warfarin isopropanol clathrate.

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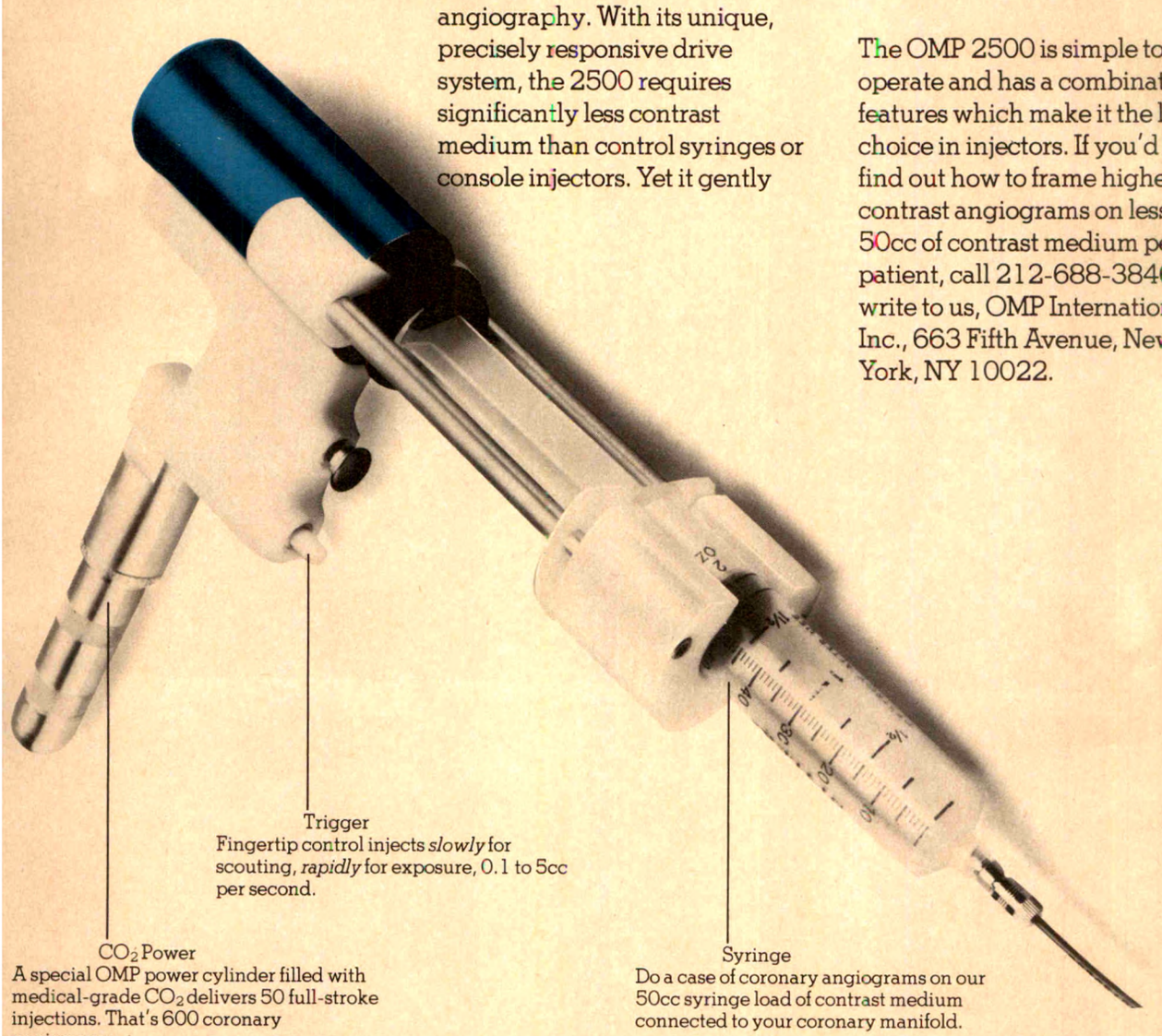
March, 1977

Introducing the 2500.

OMP's most advanced coronary angiography injector.

The OMP 2500 is a significant improvement over current injection techniques for coronary angiography. With its unique, precisely responsive drive system, the 2500 requires significantly less contrast medium than control syringes or console injectors. Yet it gently injects no faster than the human hand and with the same sensitive control.

The OMP 2500 is simple to operate and has a combination of features which make it the logical choice in injectors. If you'd like to find out how to frame higher contrast angiograms on less than 50cc of contrast medium per patient, call 212-688-3846 or write to us, OMP International, Inc., 663 Fifth Avenue, New York, NY 10022.



Trigger
Fingertip control injects *slowly* for scouting, *rapidly* for exposure, 0.1 to 5cc per second.

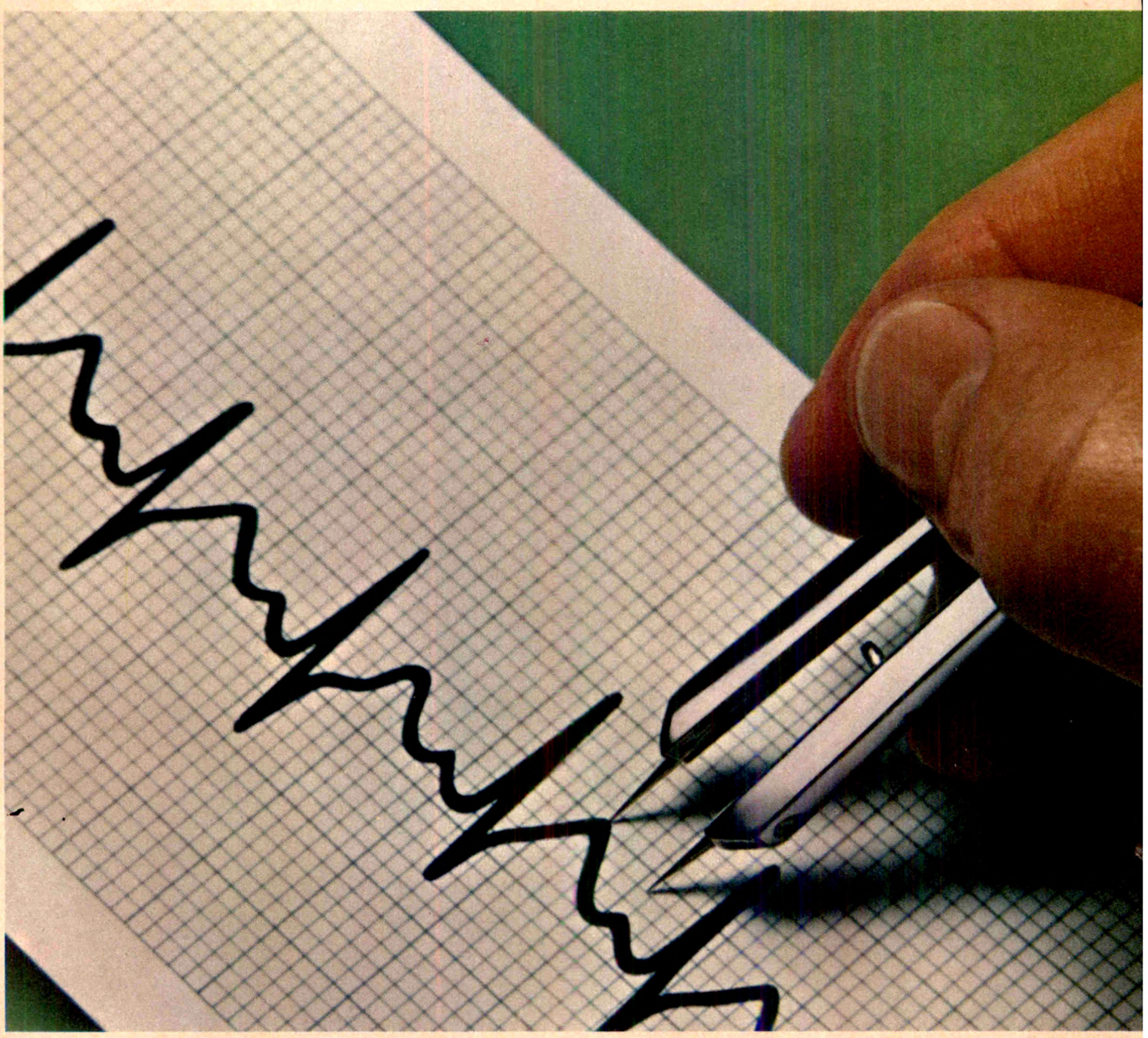
CO_2 Power
A special OMP power cylinder filled with medical-grade CO_2 delivers 50 full-stroke injections. That's 600 coronary angiograms.

Syringe
Do a case of coronary angiograms on our 50cc syringe load of contrast medium connected to your coronary manifold.

OMP
Laboratories, Inc.

INDERAL®
(propranolol hydrochloride)
PERFORMANCE IN CARDIAC ARRHYTHMIAS

EFFECTIVE ALONE OR IN COMBINATION



A116

INDERAL (propranolol hydrochloride): Successful treatment of supraventricular arrhythmias for over 10 years

INDERAL, used alone or in combination with other antiarrhythmics, has improved or resolved a variety of supraventricular arrhythmias.[1-7]

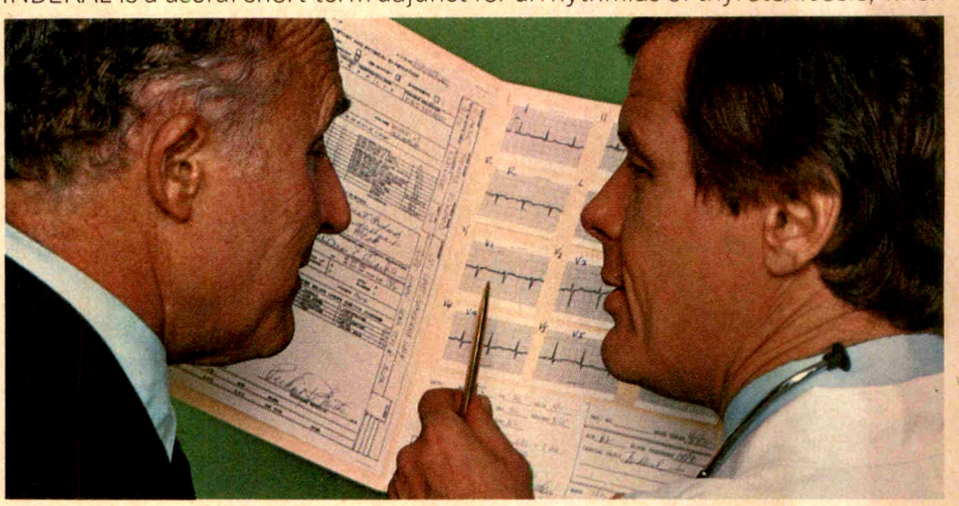
INDERAL alone: Results of use against atrial tachyarrhythmias in one series have recently been reported:

Arrhythmia	Patients	Proportion deriving benefit	
		Complete	Partial
Sinus tachycardia	86	59%	22%
Atrial tachycardia (including paroxysmal type)	154	61%	19%
Atrial flutter	50	54%	32%
Atrial fibrillation	139	53%	26%

Adapted from Coodley and Snyder.[8]

INDERAL is particularly effective in therapy of supraventricular tachyarrhythmias.[9] It slows depolarization of sinus and ectopic pacemaker cells, and retards impulse-conduction in the atria and across the AV node.[1,10,11] In cases where it cannot restore normal sinus rhythm, INDERAL is frequently effective in reducing the ventricular rate.[1-3,12-14] INDERAL may prevent recurrent supraventricular tachyarrhythmias when digitalis and quinidine fail to do so.[9,12] In addition, INDERAL is a useful short-term adjunct for arrhythmias of thyrotoxicosis, when





used with specific therapy. Since INDERAL may mask the clinical signs of hyperthyroidism, abrupt withdrawal should be avoided to prevent exacerbation of the symptoms of hyperthyroidism.

And in combination: INDERAL has also been used to complement the actions of other antiarrhythmic agents.[3-5,8,9,13] The combination of INDERAL and quinidine has suppressed supraventricular arrhythmias that have not responded to either drug alone.[3,9]

When toxic doses of digitalis glycosides occasionally fail to control the ventricular rate in patients with atrial fibrillation or flutter, addition of INDERAL to a digitalis glycoside, with reduction of the digitalis dosage, may prolong AV conduction to the point where satisfactory control of ventricular rhythm is established.[8,15]

INDERAL: Often effective in tachyarrhythmias of digitalis intoxication[2,9,10,14] INDERAL has been found useful in the treatment of certain digitalis-induced arrhythmias that persist following discontinuation of digitalis and correction of electrolyte disturbances, particularly hypokalemia. Its use in this setting may be limited by the presence of significant congestive failure or heart block, and the development of severe bradycardia. (Please see prescribing information on the next page for "Overdosage or Exaggerated Response.")

INDERAL is contraindicated in sinus bradycardia, greater than first degree heart block, and congestive heart failure unless the failure is secondary to tachyarrhythmias treatable with INDERAL. (See prescribing information for complete list of CONTRAINDICATIONS.)

Please see next page for prescribing information.

Ayerst

BRIEF SUMMARY
(For full prescribing information, see package circular.)

INDERAL® Brand of propranolol hydrochloride

A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS: INDERAL is a beta-adrenergic receptor blocking drug, possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available beta receptor sites. When access to beta receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and one-half hours. The biologic half-life is approximately two to three hours. Propranolol is not significantly dialyzable. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade and this appears to be its principal antiarrhythmic mechanism of action. The membrane effect also plays a role, particularly, some authorities believe, in digitalis-induced arrhythmias. Beta-adrenergic blockade is of unique importance in the management of arrhythmias due to increased levels of circulating catecholamines or enhanced sensitivity of the heart to catecholamines (arrhythmias associated with pheochromocytoma, thyrotoxicosis, exercise).

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential and depresses cardiac function.

INDICATIONS: Cardiac Arrhythmias

1.) Supraventricular arrhythmias

a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.)

b) Persistent sinus tachycardia which is noncompensatory and impairs the well-being of the patient.

c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy.

May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS.)

d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures.

e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

2.) Ventricular tachycardias

Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias.

a) Ventricular tachycardias

With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice. In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered. If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly. (See DOSAGE AND ADMINISTRATION.) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.*

b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

3.) Tachyarrhythmias of digitalis intoxication

If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur. (See OVERDOSAGE OR EXAGGERATED RESPONSE.)

Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION.)

4.) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia

Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, INDERAL may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. (See WARNINGS.)

Hypertrophic Subaortic Stenosis: INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of INDERAL in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.

Pheochromocytoma: After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use INDERAL (propranolol hydrochloride) unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS: INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS: CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the signs of clinical developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function: beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY: beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy, or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS: Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS: *Cardiovascular:* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION: The dosage range for INDERAL (propranolol hydrochloride) is different for each indication.

ORAL

ARRHYTHMIAS—10-30 mg three or four times daily, before meals and at bedtime.

HYPERTROPHIC SUBAORTIC STENOSIS—20-40 mg three or four times daily, before meals and at bedtime.

PHEOCHROMOCYTOMA—*Preoperatively*—60 mg daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.

—*Management of inoperable tumor*—30 mg daily in divided doses.

PEDIATRIC DOSAGE: At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS: Intravenous administration is reserved for life-threatening arrhythmias or those occurring under anesthesia. The usual dose is from 1 to 3 mg administered under careful monitoring, *e.g.*, electrocardiographic, central venous pressure. The rate of administration should not exceed 1 mg (1 ml) per minute to diminish the possibility of lowering blood pressure and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the site of action even when a slow circulation is present. If necessary, a second dose may be given after two minutes. Thereafter, additional drug should not be given in less than four hours. Additional INDERAL should not be given when the desired alteration in rate and/or rhythm is achieved.

Transference to oral therapy should be made as soon as possible.

The intravenous administration of INDERAL has not been evaluated adequately in the management of hypertensive emergencies.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg): IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY.

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS

HYPOTENSION—VASOPRESSORS, *e.g.*, LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE

HOW SUPPLIED: INDERAL (propranolol hydrochloride)

TABLETS

No. 461—Each scored tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 464—Each scored tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 468—Each scored tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

INJECTABLE

No. 3265—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 ml ampuls in boxes of 10.

REFERENCES: 1. Shand, D.G.: N. Engl. J. Med. *293*:280 (Aug. 7) 1975. 2. Conn, R.D.: Postgrad. Med. *55*(No. 2):131 (Feb.) 1974. 3. Fors, W.J., Vanderank, C.R., and Reynolds, E.W.: Am. J. Cardiol. *27*:190 (Feb.) 1971. 4. Levi, G.F., and Proto, C.: Cardiology *55*:249, 1970. 5. Stern, S.: Am. Heart J. *74*(No. 2):170 (Aug.) 1967. 6. Luna, M.H., Adelsón, E.I., and Miller, A.J.: Circulation *34*:767 (Nov.) 1966. 7. Gianelly, R.E., Griffin, J.R., and Harrison, D.C.: Ann. Intern. Med. *66*:667 (Apr.) 1967. 8. Coodley, E.L., and Snyder, S.: Am. Fam. Physician *14*(No. 5):146 (Nov.) 1976. 9. Miller, R.R., Amsterdam, E.A., and Mason, D.T.: Drug Therapy *5*:110 (Feb.) 1975. 10. Danahy, D.T., and Aronow, W.S.: Postgrad. Med. *61*(No. 1):113 (Jan.) 1977. 11. Gettes, L.S.: Med. Opinion *5*(No. 9):19 (Sept.) 1976. 12. Gianelly, R.E., and Harrison, D.C.: Geriatrics *25*:120 (Apr.) 1970. 13. Michaelson, S.P., and Wolfson, S.: Cardiovasc. Med. *1*(No. 3):213 (Nov.) 1976. 14. Wit, A.L., Hoffman, B.F., and Rosen, M.R.: Am. Heart J. *90*(No. 5):665 (Nov.) 1975. 15. Bigger, J.T., and Giardina, E.G.V.: Cardiovasc. Clin. *6*(No. 2):103, 1974.

7801

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Green light for hepatic function.

Measure liver function using Cardio-Green® (CG®) (Sterile Indocyanine Green, USP) injectable dye: A product that's been established in over 20 years of use.

The plasma disappearance of Cardio-Green shows good correlation with Bromsulphalein® (BSP®)[1] (Sulfobromophthalein Sodium Injection, USP) and *overall is a superior product* for the quantification of hepatic function and blood flow.

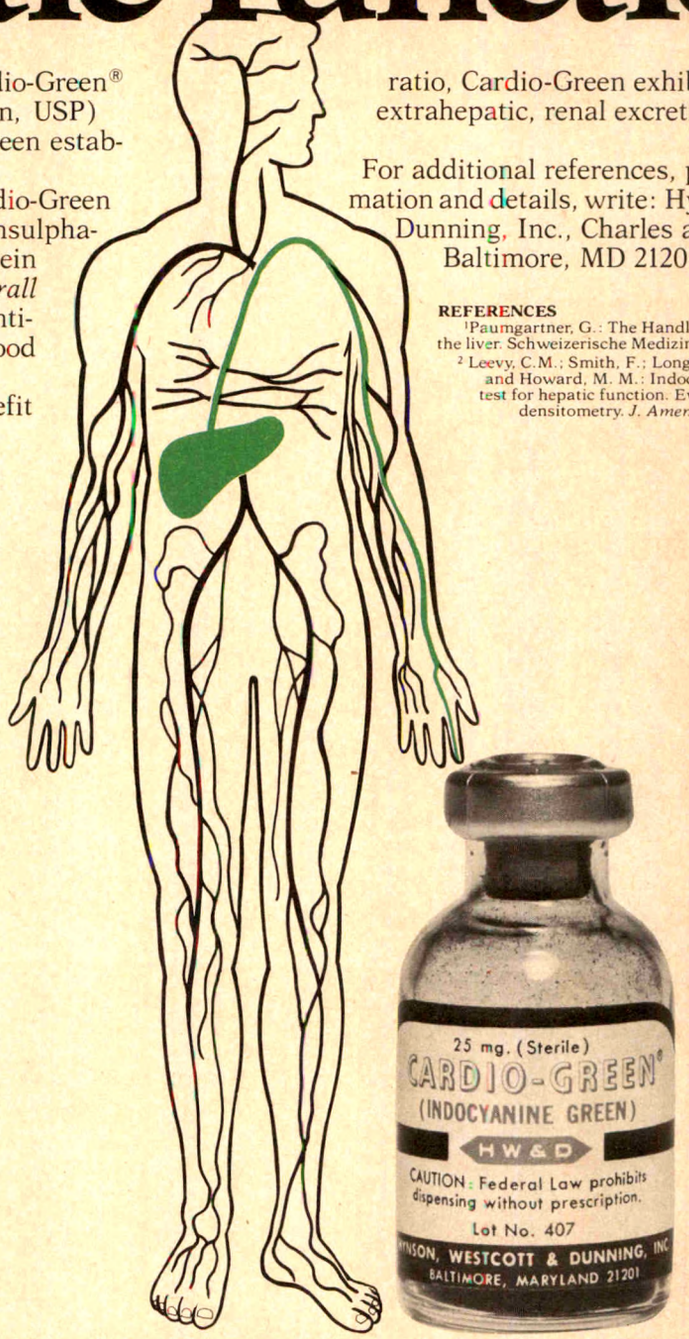
In addition to a superior risk/benefit ratio, Cardio-Green exhibits none of BSP's extrahepatic, renal excretion, and enterohepatic circulation.[2]

For additional references, professional information and details, write: Hynson, Westcott & Dunning, Inc., Charles and Chase Streets, Baltimore, MD 21201. (301) 837-0890.

REFERENCES

[1] Paumgartner, G.: The Handling of Indocyanine Green by the liver. Schweizerische Medizinische Wochenschrift (1975).

[2] Leevy, C.M.; Smith, F.; Longueville, J.; Paumgartner, G.; and Howard, M. M.: Indocyanine Green clearance as a test for hepatic function. Evaluation by dichromatic ear densitometry. *J. Amer. Med. Assn.* 200, 136 (1967).



BEFORE PRESCRIBING, PLEASE CONSULT THE INSERT WHICH ACCOMPANIES THE PRODUCT, A BRIEF SUMMARY FOLLOWS:

DESCRIPTION. Cardio-Green is a sterile, water soluble, tricarbocyanine dye with a peak spectral absorption at 800-810 nanometers in plasma or blood.

ACTION. CG permits recording of indicator-dilution curves for both diagnostic and research purposes independently of fluctutations in oxygen saturation. In the performance of dye dilution curves, a known amount of dye is usually injected as a single bolus as rapidly as possible via a cardiac catheter into selected sites in the vascular system. A recording instrument (oximeter or densitometer) is attached to a needle or catheter for sampling of the dye-blood mixture from a systemic arterial sampling site.

Ear oximetry has also been used and makes it possible to monitor the appearance and disappearance of CG without blood withdrawal.

Following intravenous injection, CG is rapidly bound to plasma protein, of which albumin is the principle carrier. It has a hepatic storage capacity of 70 mg/mg/100 ml and excretory Tm of 7.5 mg/min in healthy subjects. CG undergoes no significant extrahepatic or enterohepatic circulation; simultaneous arterial and venous blood estimations have shown negligible renal, peripheral, lung or cerebrospinal uptake of the dye. CG is taken up from the plasma almost exclusively by the hepatic parenchymal cells and is secreted entirely into the bile. After biliary obstruction, the dye appears in the hepatic lymph, independently of the bile, suggesting that the biliary mucosa is sufficiently intact to prevent diffusion of the dye, though allowing diffusion of bilirubin. These characteristics make CG a helpful index of hepatic function.

INDICATIONS. For determining cardiac output, hepatic function and liver blood flow and ophthalmic angiography.

CONTRAINDICATIONS. The safe use of Cardio-Green during pregnancy has not been established.

WARNINGS. CG Powder and Solution: CG is unstable in aqueous solution and must be used within 10 hours. However, the dye is stable in plasma and whole blood so that samples obtained in discontinuous sampling techniques and stored at 2-8° may be read within a 2-day period. Sterile techniques should be used in handling the dye solution as well as in the performance of the dilution curves.

PRECAUTIONS. Probenecid in doses of from 25 to 100 mg/kg has been shown to affect the hepatic uptake, storage and removal of CG in dogs; this has not been reported in humans, but should be considered.

ADVERSE REACTIONS. CG contains a small amount of sodium iodide and should be used with caution in patients who have a history of allergy to iodides. Radioactive iodine uptake studies should not be performed for at least a week following the use of CG.

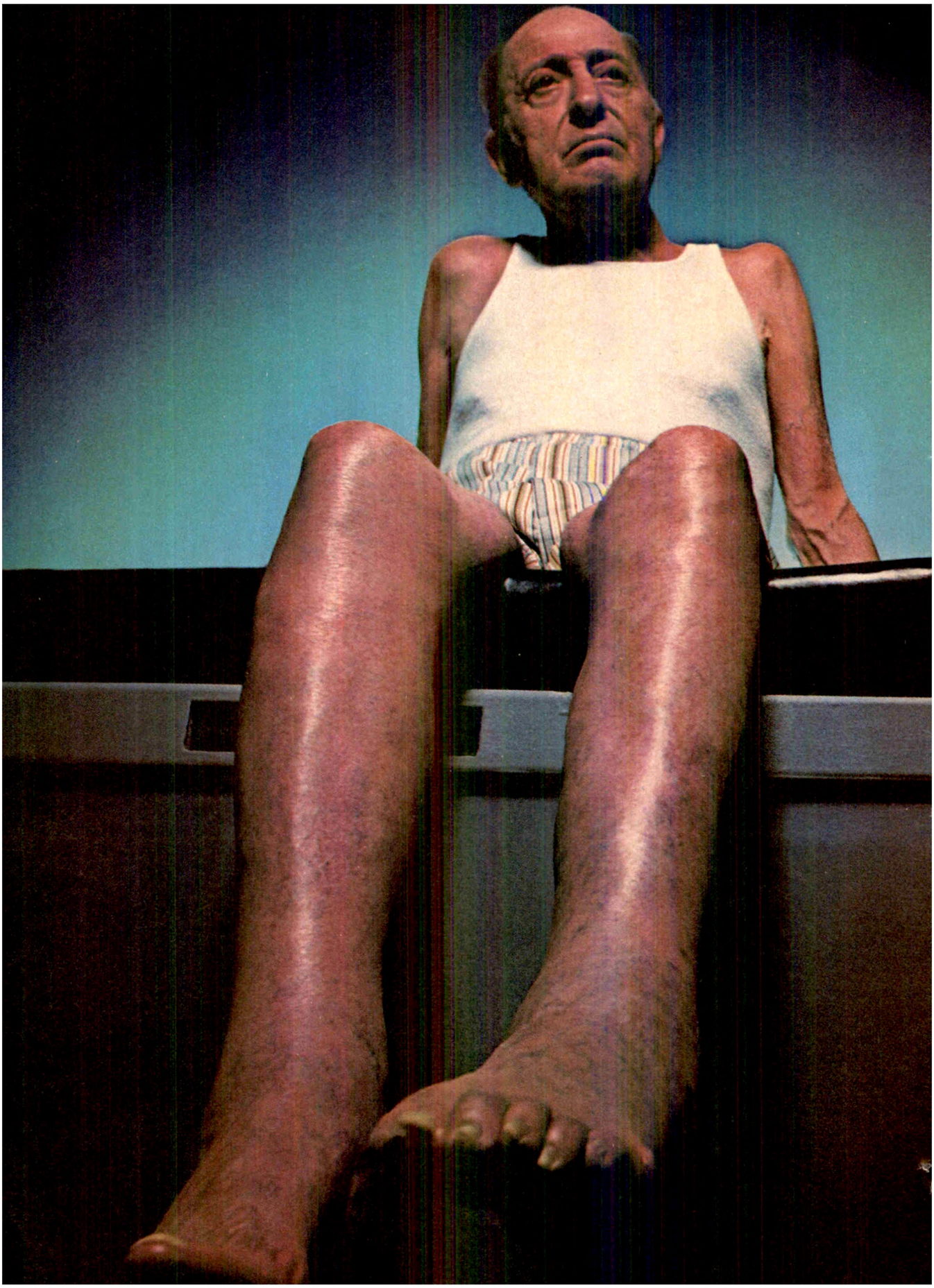
DOSAGE AND ADMINISTRATION. The usual dosages of CG are as follows: for dilution curves, Adults—5 mg, Children—2.5 mg, and Infants—1.25 mg; for hepatic function, 0.5 mg per kg of body weight.

HEPATIC FUNCTION STUDIES. Due to its absorption spectrum, changing concentrations of Cardio-Green (Sterile Indocyanine Green, USP) in the blood can be monitored by ear densitometry or by obtaining blood specimens for photometric determination using percentage retention of dye from a single 20-minute sample or using disappearance rate at timed intervals. The technique for both methods is described in the instructions, which accompany the product.

NORMAL VALUES. Percentage disappearance rate in healthy subjects is 18-24% per minute. Normal biological half-time is 2.5-3.0 minutes.

SUPPLIES. A 25 mg vial (NDC 0011-8361-20) and 50 mg vial (NDC 0011-8362-55) and 10 mg (NDC 0011-8363-72) and 40 mg (NDC 0011-8364-54) CG Single Use Unit, with calibrated syringes. All put-ups with aqueous solvent.

Bromsulphalein, BSP, Cardio-Green, CG, Hynson, Westcott & Dunning, Inc. and ◆ are trademarks of Hynson, Westcott & Dunning, Inc.



In cardiac edema...

the diuretic most likely to succeed.

It can outperform the thiazides in sodium loss

Lasix® (furosemide) has a greater potential for ridding the body of excess sodium and water than any other commonly used diuretic. A potential that has been realized in multiple comparative studies in patients with cardiac edema.

That's why Lasix is the diuretic most likely to succeed in all degrees of cardiac edema.

It need not go beyond them in potassium loss

With Lasix, the key to minimizing electrolyte disturbances is proper dosage. For if you control the cardiac patient's urine output and edema by titrating the dosage, the result likely will be excretion of less potassium because Lasix produces a dilute urine. As with any diuretic, electrolyte depletion can occur during therapy with furosemide. Careful clinical and laboratory observations are recommended.

And it often works where thiazides can't

Unlike other commonly used diuretics, Lasix can be useful in patients with severely depressed renal function. Even in the presence of renal insufficiency with acidosis, alkalosis or hypoalbuminemia, Lasix has been found both effective and well tolerated. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the drug should be discontinued. Lasix is contraindicated in anuria.

The basic unit–
for initial therapy.
40 mg tablets.

The adjuster unit–
for maintenance therapy.
20 mg tablets.

LASIX® (furosemide)

A brief summary of the Prescribing Information for Lasix (furosemide).

WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.

Indications: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs. Patients not adequately controlled with thiazides probably will not be adequately controlled with furosemide.

Contraindications: Because animal reproductive studies have shown that furosemide may cause fetal abnormalities, the drug is contraindicated in women of childbearing potential. Anuria. Continued use if increasing azotemia and oliguria occur during treatment of severe progressive renal disease. Hepatic coma. Electrolyte depletion. History of hypersensitivity to the compound.

Warnings: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Perform frequent serum electrolyte, CO_2 and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. **Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital.** Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions.

Precautions: As with any potent diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Since furosemide potentiates the effect of antihypertensive medications, reduce the dose of these agents when furosemide is administered to edematous hypertensive patients. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Cases of tinnitus and reversible hearing impairment have been reported when parenteral furosemide therapy preceded oral use. There are also reports of irreversible hearing impairment. Usually, ototoxicity has been reported when doses of furosemide exceeding several times the usual recommended dose were injected rapidly in patients with severe impairment of renal function who were also often receiving other drugs known to be ototoxic. If the physician elects to use high dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, it has been reported that an infusion rate not exceeding 4 mg furosemide per minute has been used.) Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Exercise great caution in administering curare or its derivatives to patients undergoing furosemide therapy, and it is advisable to discontinue furosemide for one week prior to any elective surgery.

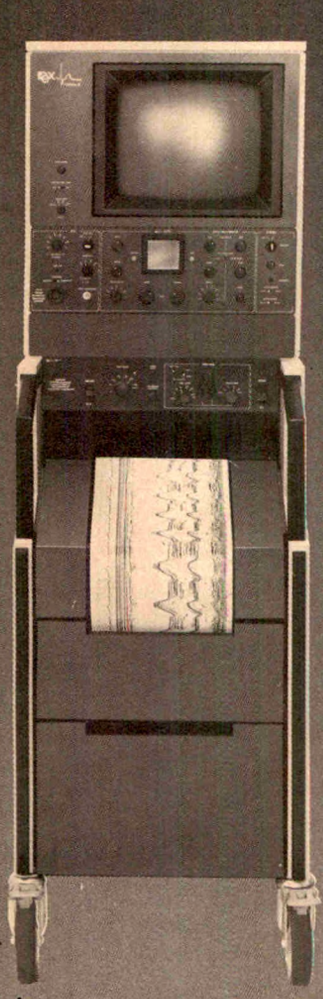
Adverse Reactions: Various forms of dermatitis, urticaria and rare forms of exfoliative dermatitis, erythema multiforme, pruritus, paresthesia, blurring of vision, postural hypotension, nausea, vomiting, or diarrhea. Anemia, leukopenia, aplastic anemia, and thrombocytopenia (with purpura). Rare cases of agranulocytosis, which responded to treatment. Although relationship to the drug has not been established with certainty, the following rare adverse reactions have been reported: sweet taste, oral and gastric burning, paradoxical swelling, headache, jaundice, thrombophlebitis and emboli, and acute pancreatitis. Furosemide-induced diuresis may be accompanied by weakness, fatigue, light-headedness or dizziness, muscle cramps, thirst, increased perspiration, urinary bladder spasm, and symptoms of urinary frequency.

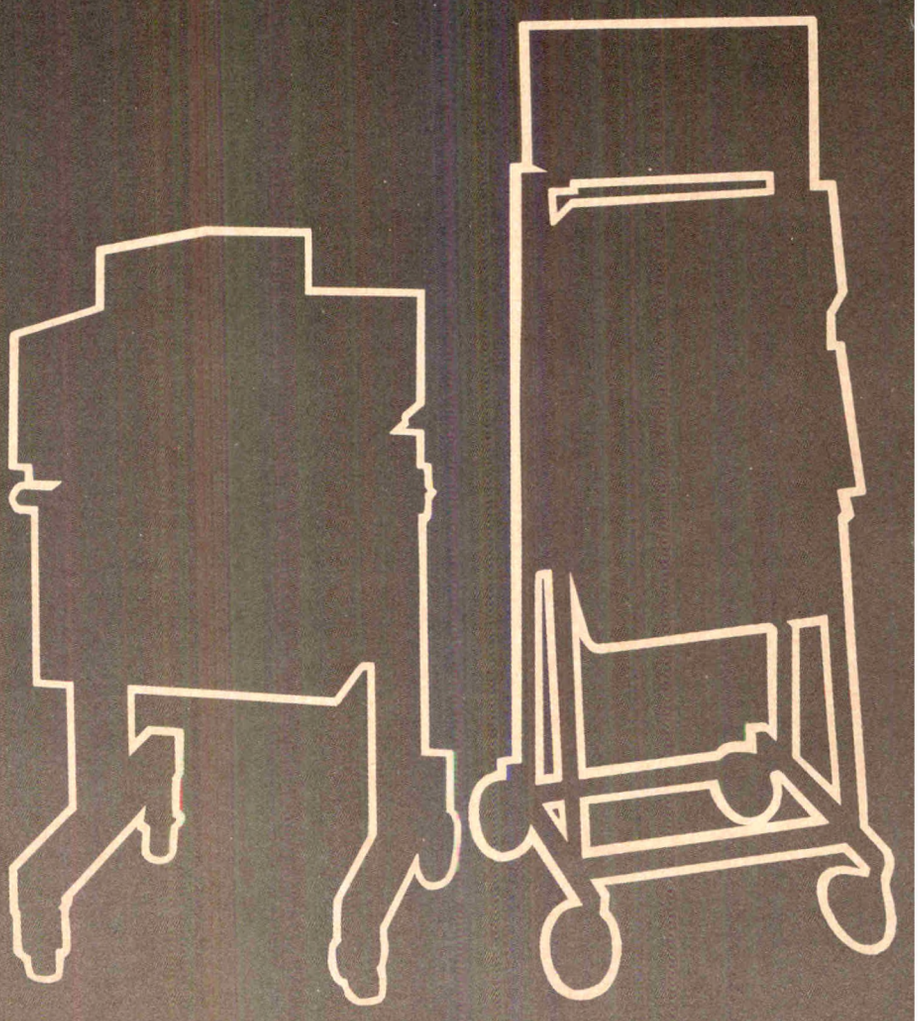
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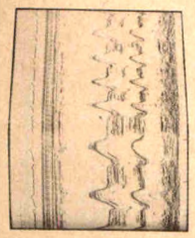
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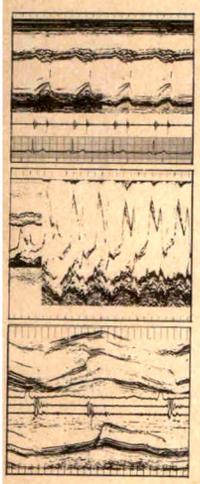
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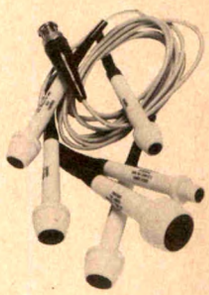


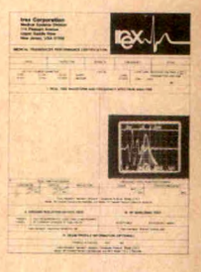
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ALDACTONE®
(spironolactone) 25 mg. tablets

WARNING
Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats (see *Warnings*). Aldactone should be used only in those conditions described under *Indications*. Unnecessary use of this drug should be avoided.

Indications: Diagnosis and treatment of primary hyperaldosteronism. Essential hypertension, edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate. Cirrhosis of the liver accompanied by edema and/or ascites. Hypokalemia.

Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, or hyperkalemia.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactone. Do not administer concurrently with other potassium-sparing diuretics.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75, and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hyponatremia may be caused or aggravated, especially when Aldactone is administered in combination with other diuretics. Transient elevation of BUN and/or mild acidosis may occur. Aldactone potentiates the effect of other diuretics or antihypertensive agents, particularly ganglionic blocking agents; therefore the dosage of such drugs should be reduced by at least 50 percent when adding Aldactone. Gynecomastia may develop and in rare instances some breast enlargement may persist. Vascular responsiveness to norepinephrine may be reduced.

Spironolactone may cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazard to the fetus. Breast feeding should be discontinued when Aldactone is being used.

Adverse Reactions: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established. Adverse reactions are usually reversible upon discontinuation of the drug.

Dosage and Administration

For primary hyperaldosteronism: 400 mg. daily for three to four weeks (long test), or for four days (short test). For preparation for surgery or for long-term maintenance therapy, 100 to 400 mg. daily.

For edema in adults: Initial daily dosage is 100 mg. in divided doses but may range from 25 to 200 mg. daily. If after five days an adequate diuretic response has not occurred, a second diuretic which acts more proximally in the renal tubule may be added. The dosage of Aldactone should remain unchanged when other diuretic therapy is added.

For edema in children: Initial daily dosage should provide approximately 1.5 mg. per pound of body weight (3.3 mg./kg.) in divided doses.

For essential hypertension: Initial adult daily dosage of 50 to 100 mg. in divided doses, alone or with diuretics which act more proximally in the renal tubule, or with other antihypertensive agents. Continue treatment for at least two weeks since maximal response may not occur before this time. Adjust subsequent dosage according to patient response.

For hypokalemia: 25 to 100 mg. daily in divided doses.

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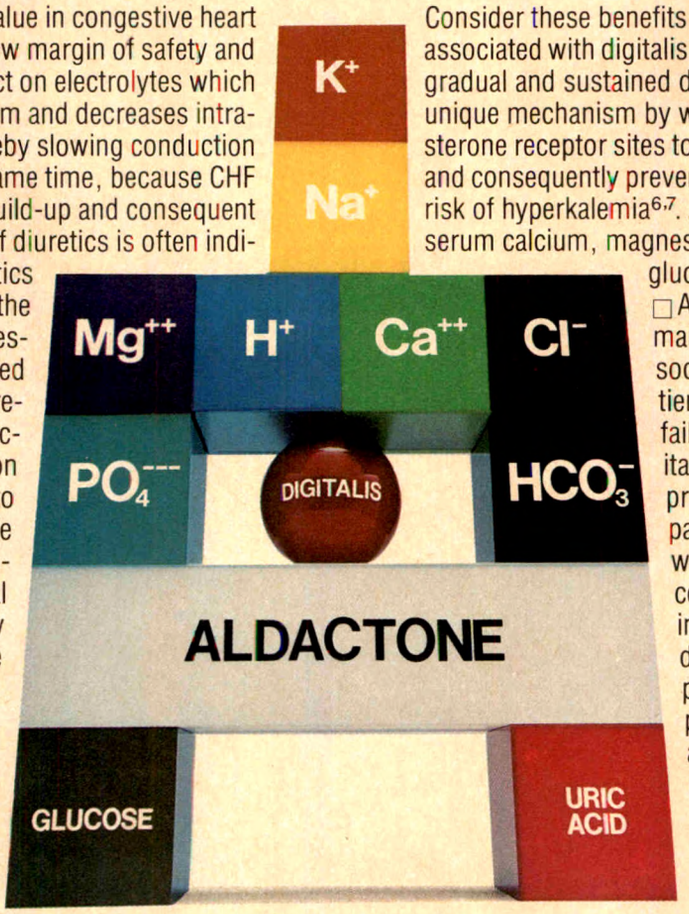
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719

The Delicate Balance.

Unfortunately, electrolyte imbalance is often a problem during digitalis therapy. And most diuretics worsen the problem.

Despite its therapeutic value in congestive heart failure, digitalis has a narrow margin of safety and toxic levels produce an effect on electrolytes which increases intracellular sodium and decreases intracellular potassium, thereby slowing conduction in cardiac tissues. At the same time, because CHF encourages sodium build-up and consequent edema, concomitant use of diuretics is often indicated. □ Use of most diuretics can increase problems for the patient on digitalis, and excessive loss of potassium caused by potent diuretics is a frequent cause of digitalis toxicity.[1,2] Potassium depletion sensitizes the myocardium to digitalis and can set the stage for serious cardiac arrhythmias even with normal dosage.[3] □ Clearly, any diuretic choice should be carefully analyzed for its effect on electrolyte balance. Thiazides, for example, can induce hypokalemia, hypercalcemia, hypomagnesemia, and hypophosphatemia.[4] They can also decrease uric acid excretion and impair glucose tolerance. In treatment with furosemide, too, fluid and electrolyte imbalance is the most common form of clinical toxicity.[5]



Fortunately, concomitant diuretic therapy with Aldactone® (spironolactone) can help maintain the delicate electrolyte balance... when other measures won't do.

Consider these benefits in avoiding the problems associated with digitalis therapy: Aldactone provides gradual and sustained diuresis...works through a unique mechanism by which it competes for aldosterone receptor sites to normalize body potassium, and consequently prevents hypokalemia with limited risk of hyperkalemia[6,7]...does not adversely affect serum calcium, magnesium and uric acid levels or glucose tolerance.[7]

□ Aldactone is indicated for management of edema and sodium retention in those patients with congestive heart failure who are taking digitalis, or in the treatment or prevention of hypokalemia in patients taking digitalis, when other measures are considered inadequate or inappropriate. □ When diuretic therapy is indicated, prescribe Aldactone to help preserve the delicate balance of electrolytes during digitalis therapy.

1. Kirkendall, W.M.: What's With Hypertension These Days? Consultant *11*:13-15 (Jan.) 1971.
2. Maronde, R.F., Milgrom, M. and Dickey, J.M.: Potassium Loss with Thiazide Therapy, Am. Heart J. *78*:16-21 (July) 1969.
3. Cardiac Glycosides, Section 4, in Kastrup, E. K. (Editor): Facts and Comparisons, St. Louis, Facts and Comparisons, Inc., Jan. 1975, pp. 140-141C.
4. Weibert, R. T.: Heading Off Adverse Reactions. Thiazide Diuretics, Curr. Prescr. *8*:62-69 (Oct.) 1977.
5. Mudge, G. H., Diuretics and Other Agents Employed in the Mobilization of Edema Fluid, Chapter 39, in Goodman, L. S., and Gilman, A. (Editors): The Pharmacological Basis of Therapeutics, ed. 5., New York, Macmillan Publishing Co., Inc., 1975, pg. 836.
6. Laragh, J. H.: Diuretics in the Management of Congestive Heart Failure, Hosp. Pract. *5*:43-50 (Nov.) 1970.
7. Tobian, L. J., Jr.: The Clinical Approach to Essential Hypertension, Hosp. Pract. *10*:33-44 (July) 1975.

SEARLE

Aldactone®

(spironolactone) 25 mg. tablets

Before prescribing, please consult the complete prescribing information, a brief summary of which follows.

New wide-angle probe for EkoSector I.™



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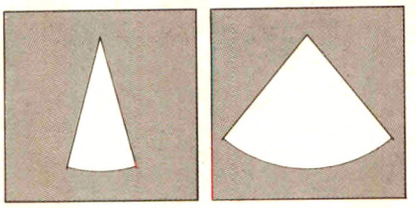
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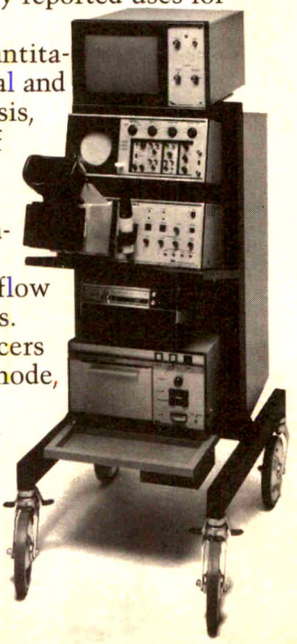
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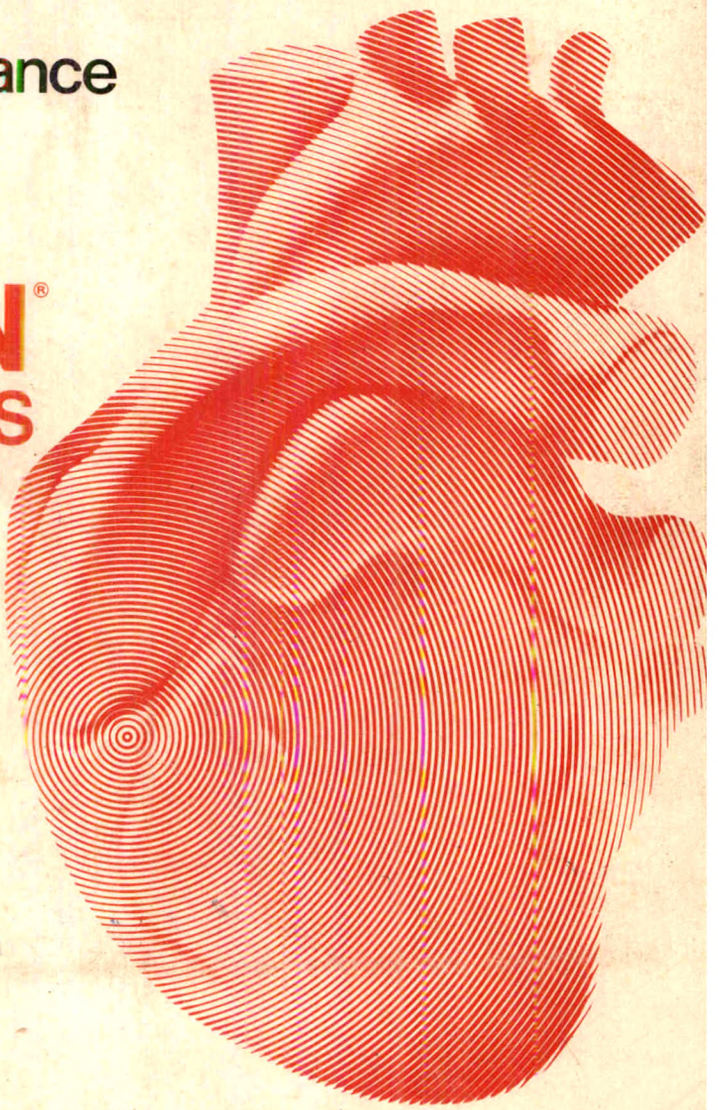
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- ☐ Convenient B.I.D. or T.I.D. dosage for most patients

CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm—whether with CARDIOQUIN Tablets or electroconversion—only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases.

Well-tolerated, CARDIOQUIN Tablets are particularly suited for maintenance therapy, since the polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 50.

Purdue Frederick

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MAY 1, 1978

The American Journal of CARDIOLOGY®

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Studies on Hypertrophic Cardiomyopathy

Effects of Lidocaine and Propranolol on Myocardial Infarction

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Contents on Page A6

A YORKE MEDICAL JOURNAL

A New Vision of Catapres® (clonidine HCl)

20/20



The first 20 days

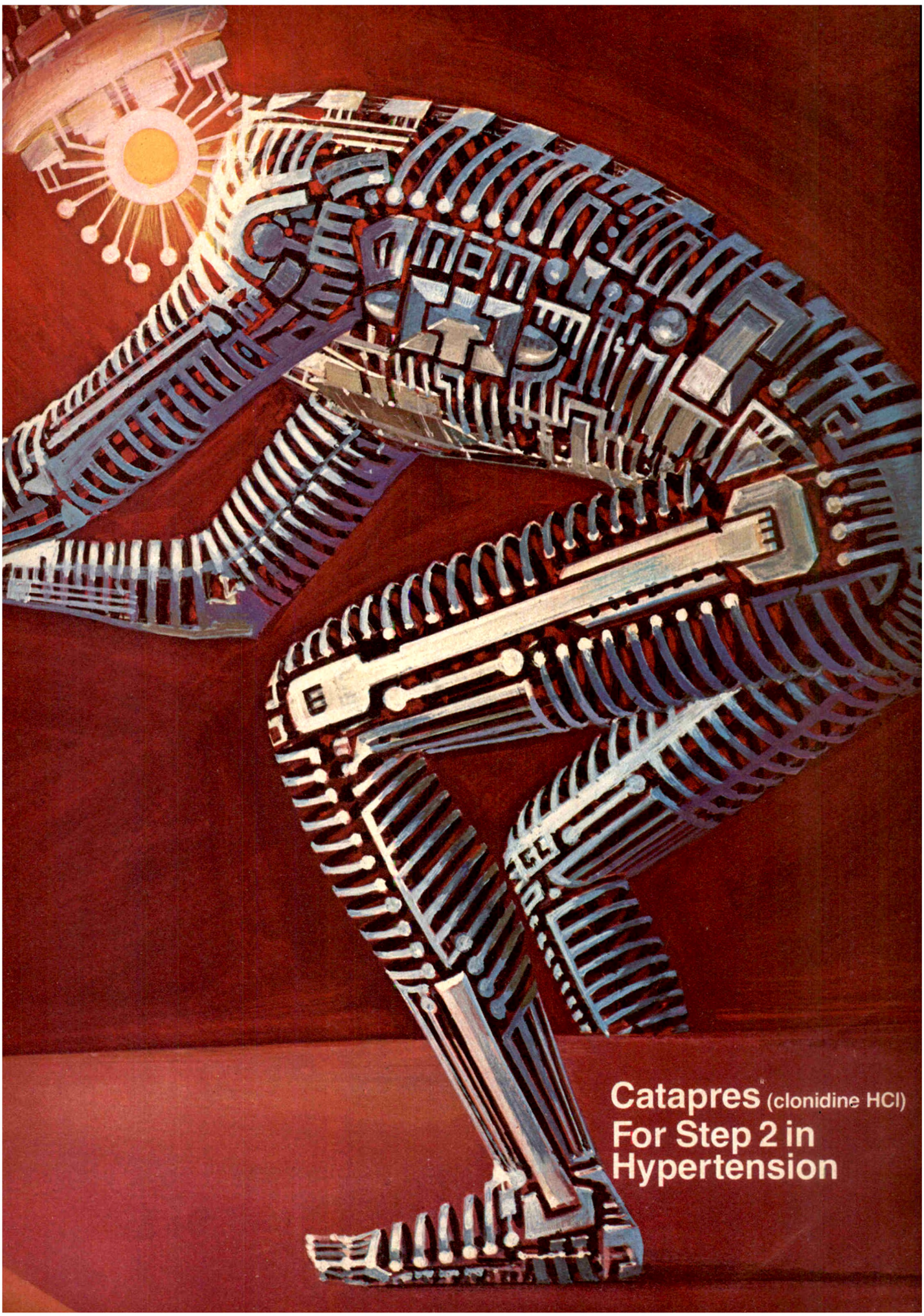
- Catapres lowers blood pressure promptly.
- No contraindications.
- Some patients may have dry mouth, drowsiness, and sedation. Tell them that these tend to diminish with continued use.
- Giving the larger part of the divided dose at bedtime can help alleviate drowsiness and sedation.

The next 20 years*

- Lowered blood pressure.
- Little impotence, depression or postural hypotension.
- No fatal hepatotoxicity in over a decade of worldwide use.
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*Tolerance may develop in some patients, necessitating a reevaluation of therapy.

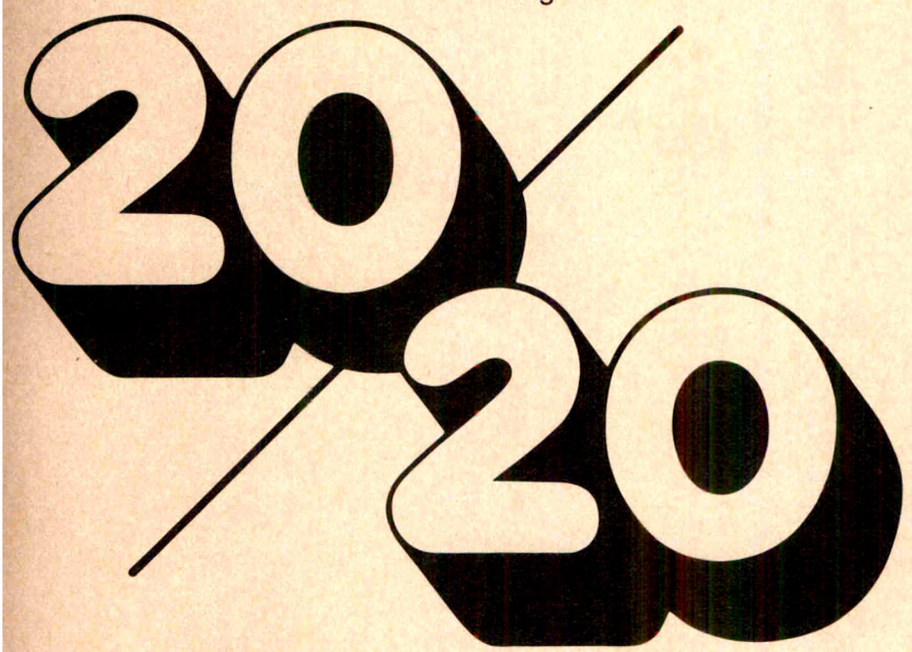
For full details on adverse reactions, warnings, and precautions, see brief summary of the prescribing information on last page of this advertisement.


Catapres (clonidine HCl)
For Step 2 in
Hypertension

HYPERTENSION

A New Vision of Catapres® (clonidine HCl)

Tablets of 0.1 and 0.2 mg



What you do the first 20 days Can help him the next 20 years

Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in poten It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings i animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetu *Usage in Children:* No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consultin their physician. Rare instances of hypertensive enceph lopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pres sure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machiner or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any oth agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established. These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patien receiving clonidine hydrochloride, chlorthalidone, and papaverine hydrochloride. Weight gain, transient eleva tion of blood glucose, or serum creatine phosphokinas congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and menta depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000.

For complete details, please see full prescribing information.

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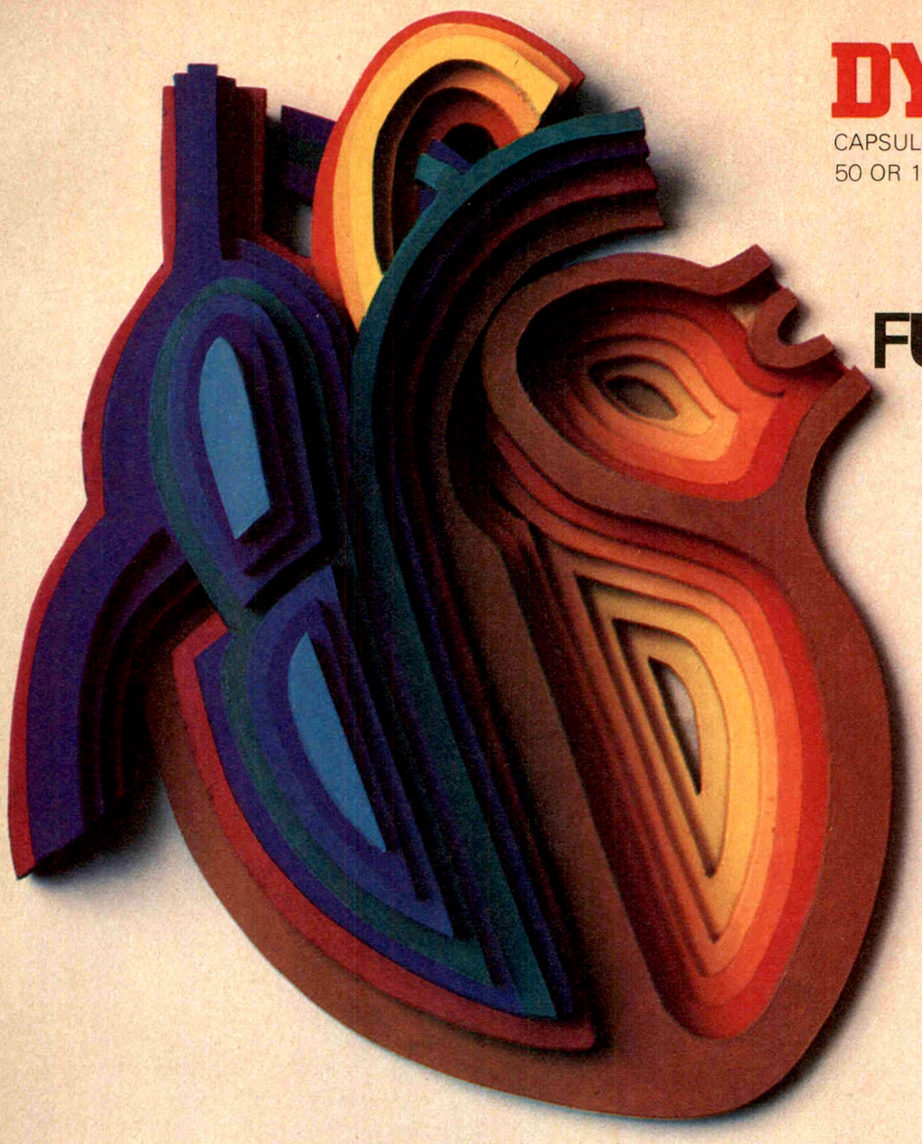
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Contraindications: Anuria. Severe or progressive kidney disease or dysfunction. Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity. Continued use in developing hyperkalemia. Do not give potassium supplements, either by drug or by diet.

Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy requires weighing anticipated benefits against possible hazards to the fetus, including adverse reactions which have occurred in the adult. Triamterene may appear in breast milk. If its use is essential, the patient should stop nursing. 'Dyrenium' and spironolactone are not usually used concurrently; if they are, however, frequent serum potassium determinations are required.

Precautions: If hyperkalemia develops, withdraw the drug. The following may also occur: electrolyte imbalance, low-salt syndrome (with low salt intake), reversible mild nitrogen retention, decreasing alkali reserve with possible metabolic acidosis. Triamterene is a weak folic acid antagonist. Do periodic hematologic studies in cirrhotics with splenomegaly. Concomitant use with antihypertensive drugs may result in an additive hypotensive effect. When 'Dyrenium' is to be discontinued after intensive or prolonged therapy, withdraw gradually because of possible rebound kaliuresis.

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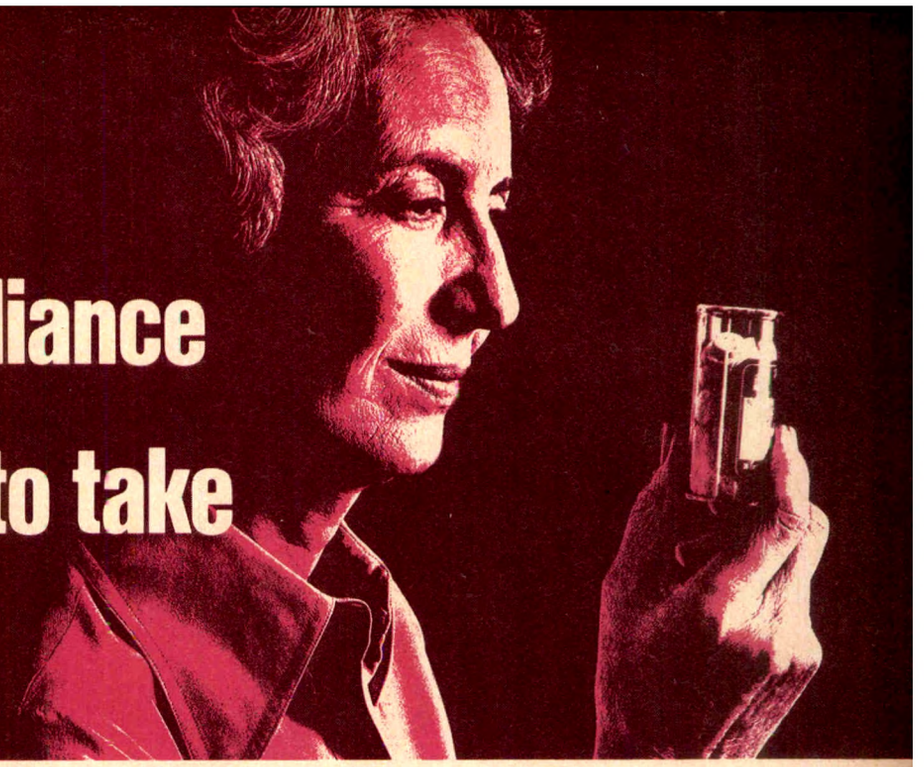
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NOTE: Depending upon the response desired, the dosage may need to be varied and the blood level and/or electrocardiographic response closely monitored during initial treatment.

Contraindications: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.

Partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. Renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects; ventricular premature beats, ventricular tachycardia or flutter while on the drug. Marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis. Idiosyncrasy or hypersensitivity to quinidine.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate.

Precautions: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy.

Quinidine in large doses may reduce the contractile force of the heart; therefore, extreme caution should be exercised in using the drug in patients with severe heart disease, hypotension or digitalis intoxication.

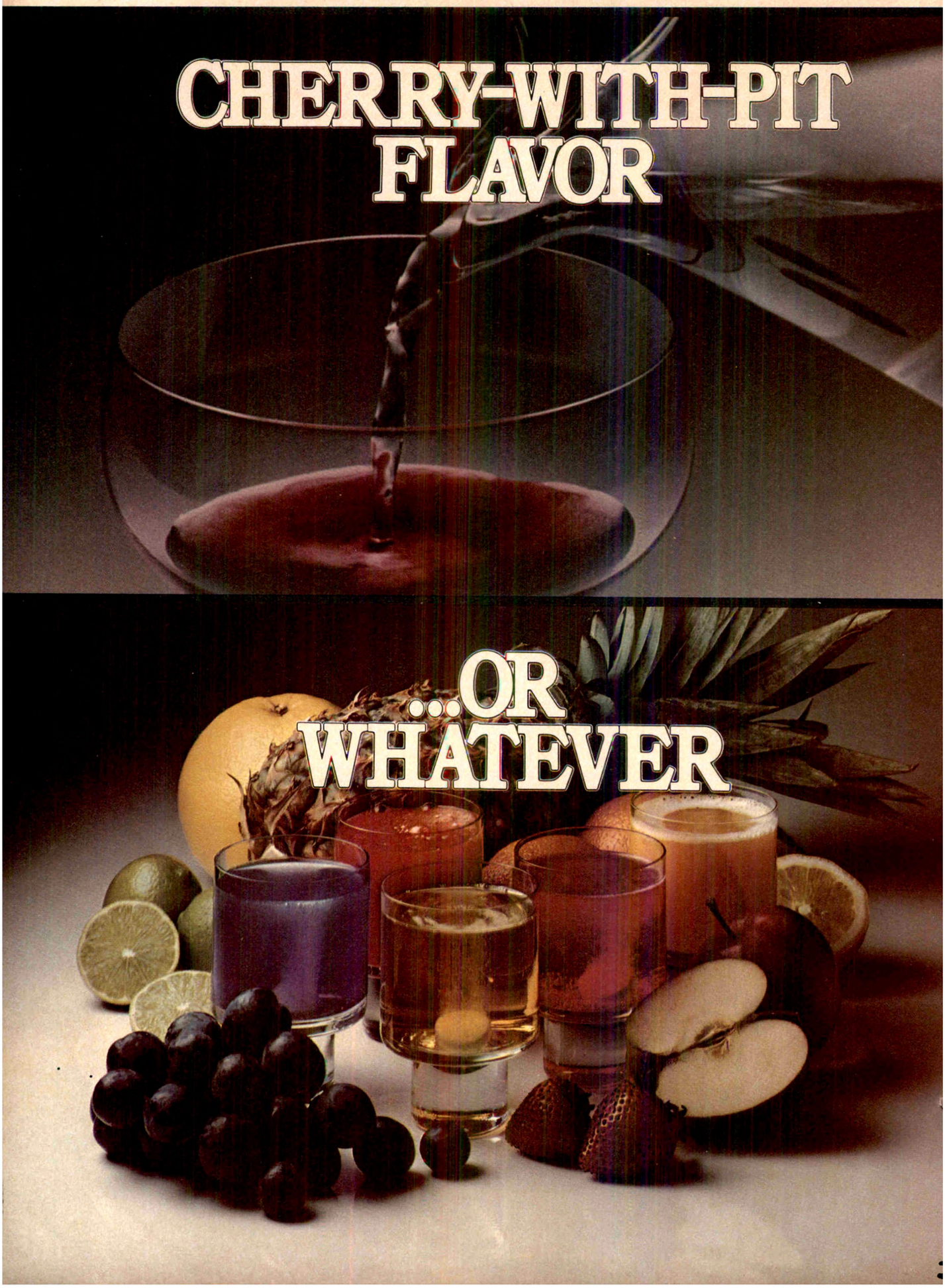
It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

Adverse Reactions: Cinchonism, tinnitus, decreased auditory acuity, vertigo, headache, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis, hypotension, respiratory distress, and gastrointestinal disturbances.

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Description: Klorvess Effervescent Tablets: Each dry, sodium- and sugar-free effervescent tablet contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g. Dissolution of the tablet in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

Indications: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

Contraindications: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements.

Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis.

High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest.

To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve each Klorvess Effervescent Tablet in 3 to 4 ounces of water or fruit juice, or dilute each tablespoonful of Klorvess (potassium chloride) 10% Liquid in 3 to 4 ounces of water. Both of these solutions should be ingested slowly with or immediately after meals.

Adverse Reactions: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts.

The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest.

The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

Dosage and Administration: Klorvess Effervescent Tablets: Adults—One Klorvess Effervescent Tablet (20 mEq each of potassium and chloride) completely dissolved in 3 to 4 ounces of cold water or fruit juice 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) of Klorvess Liquid (20 mEq of potassium chloride) completely diluted in 3 to 4 ounces of water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating. Deviations from these recommended dosages may be indicated in certain cases of hypokalemia based upon the patient's status. The average total daily dosage must be governed by the patient's response as determined by frequent evaluation of serum electrolytes, EKG and clinical status.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

Treatment of Hyperkalemia: 1. Dextrose solution, 10 or 25% containing 10 units of crystalline insulin per 20 g dextrose, given IV in a dose of 300 to 500 ml in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resins, orally and as retention enema. (Caution: Ammonium compounds should not be used in patients with hepatic cirrhosis.) 3. Hemodialysis and peritoneal dialysis. 4. The use of potassium-containing foods or medicaments must be eliminated. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

How Supplied: Klorvess Effervescent Tablets (white)—60 tablets (2 Rx units of 30 effervescent tablets each). Each tablet is individually foil wrapped. Klorvess (potassium chloride) 10% Liquid (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Tablets and Liquid are also available in institutional packaging as follows: Klorvess Tablets—30 and 1000 tablets; Klorvess Liquid—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

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CLINICAL STUDIES

803 Sudden Death in Patients with Hypertropic Cardiomyopathy: Characterization of 26 Patients Without Functional Limitation

BARRY J. MARON, WILLIAM C. ROBERTS, JESSE E. EDWARDS, HUGH A. McALLISTER Jr., DANIEL D. FOLEY and STEPHEN E. EPSTEIN

Sudden death is not rare in patients with hypertrophic cardiomyopathy and no previous functional limitations. Children and young adults appear particularly susceptible to sudden death, 23 of the 26 patients in this study being less than 25 years old at death. Characteristic of this group at high risk for death were a distinctly abnormal electrocardiogram and a moderately to severely thickened ventricular septum. No other clinical or hemodynamic variable was an entirely reliable predictor of death in these patients. Six patients showed electrocardiographic evidence of increasing left ventricular overload within 4 years of the time of death. Although the exact mechanism of sudden death is unknown, ventricular arrhythmias are suggested as the terminal event; it was documented in four patients immediately after their collapse. The data suggest that atrial arrhythmias also played an etiologic role in the precipitation of ventricular fibrillation in some subjects.

811 Electrophysiologic Findings in Patients With Idiopathic Hypertrophic Subaortic Stenosis

ROBERT E. INGHAM, JAY W. MASON, RONALD M. ROSSEN, DANIEL J. GOODMAN and DONALD C. HARRISON

Intracardiac electrophysiologic studies in 13 subjects with proved idiopathic hypertrophic subaortic stenosis, a large incidence of arrhythmias and conduction system abnormalities showed normal P-A and A-H intervals in all, prolonged H-V intervals greater than 50 msec in 10 of 12 patients (83 percent) and greater than 60 msec in 7 (58 percent). Dual A-V nodal responses were evoked with propranolol in three patients and persisted in four other patients with dual responses despite propranolol administration. The extent and distribution of these electrophysiologic responses, in part related to abnormal myocardium typical of this disease, may play a significant role in the arrhythmias and conduction abnormalities that a patient with idiopathic hypertrophic subaortic stenosis may experience. The large incidence of abnormalities in the distal specialized conduction system, heretofore unrecognized, has potentially important prognostic and therapeutic implications.

817 Inferior Myocardial Infarction as a Cause of Asymmetric Septal Hypertrophy. An Echocardiographic Study

HARTMUT HENNING, ROBERT A. O'ROURKE, MICHAEL H. CRAWFORD, ALBERTO RIGHETTI and JOEL S. KARLINER

Increased septal thickness on echocardiography following an inferior wall myocardial infarction may cause an abnormal septal to posterior wall thickness ratio of greater than 1.3 that meets the current echocardiographic criterion for asymmetric septal hypertrophy. In these 68 patients 2 or more months after a single transmural myocardial infarction, M mode echocardiography revealed a greater septal to posterior wall thickness ratio in those with inferior infarction than in those with anterior infarction. This greater septal to posterior wall ratio in 22 of the 42 patients with previous inferior wall infarction and in only 1 of the 26 patients with prior anterior wall infarction was associated with increased septal thickness in the majority (78 percent) of patients rather than a thinner left ventricular posterior wall.

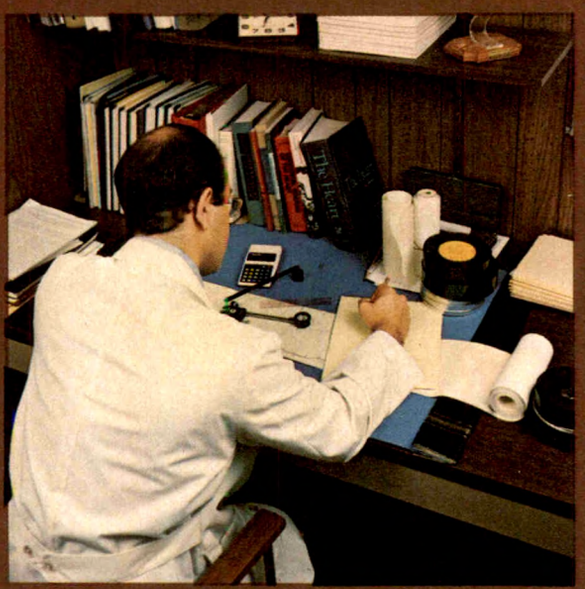
823 Early Systolic Closure of the Aortic Valve in Patients With Hypertrophic Subaortic Stenosis and Discrete Subaortic Stenosis. Correlation With Preoperative and Postoperative Hemodynamics

ZVONIMIR KRAJCER, FULVIO ORZAN, LEONARD W. PECHACEK, EFRAIN GARCIA and ROBERT D. LEACHMAN

Echocardiographic analysis of the patterns of motion of the aortic valve revealed early systolic closure of one or both aortic cusps in 9 patients with discrete subaortic stenosis and in 22 patients with idiopathic hypertrophic

Continued on page A14

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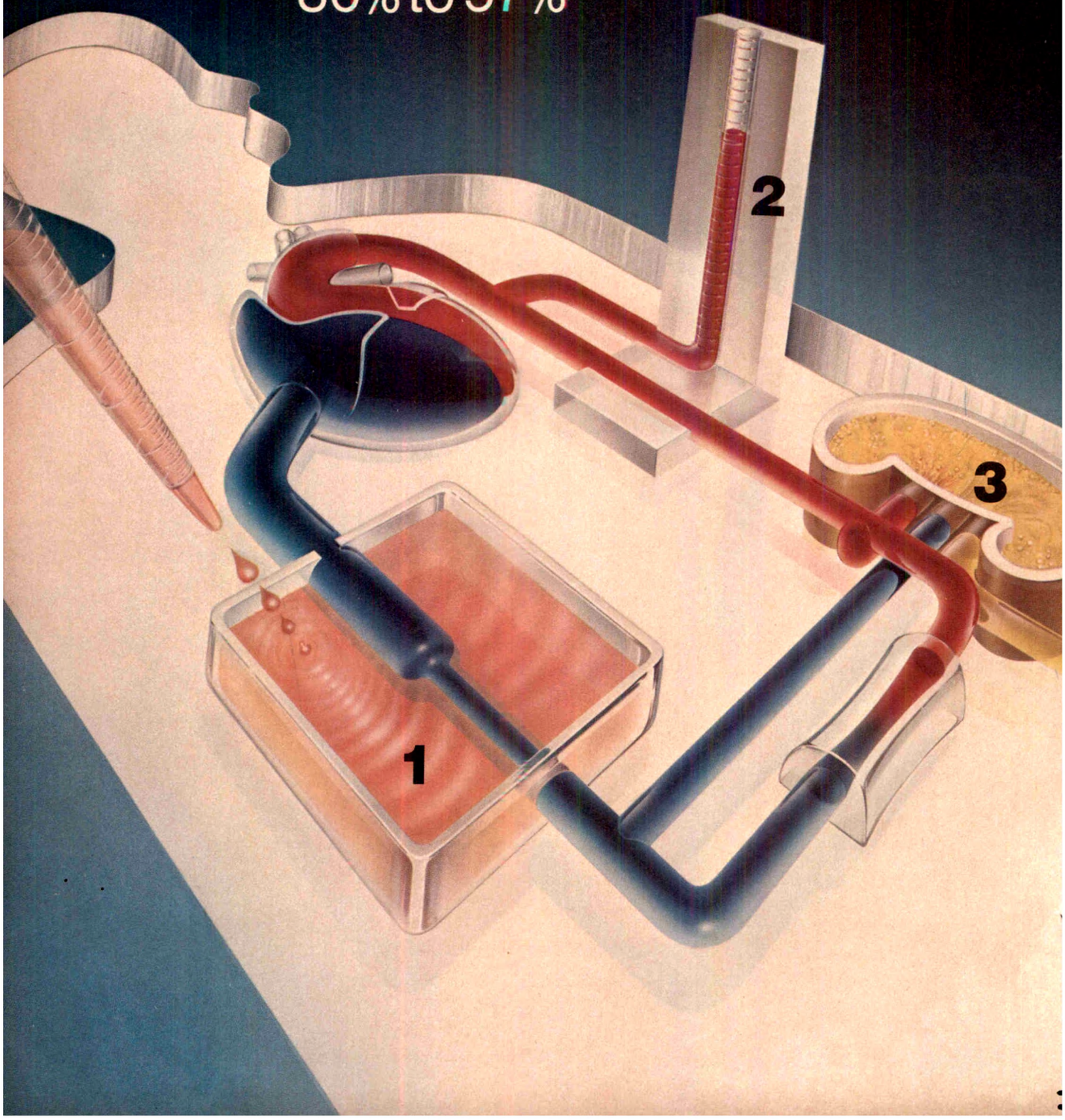
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*All values given in this example are approximations based on standard physiologic data and solute-volume relationships.

†From a baseline of 80 mm. Hg diastolic.

BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema.

Contraindications: Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.

Warnings: Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.

Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

Adverse Reactions: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

Usual Dose: One tablet daily.

How Supplied: Tablets—100 mg. (white, scored) and 50 mg. (aqua) in bottles of 100 and 1000; PAKs of 28 tablets, boxes of 6; unit-dose blister packs, boxes of 100 (10 x 10 strips).

References:

1. Guyton, A.C.: Regulation of arterial pressure: II. The renal-body fluid system for long-term pressure control. Mechanisms of hypertension, in Textbook of Medical Physiology, Philadelphia, Saunders, 1976, p. 281. **2.** Kaplan, N.: Treating hypertension: The results are in, in Mandates Hypertension (Kaplan, N.M., ed.), New York, Medcom, 1976, p. 6. **3.** Finnerty, F.A., Jr.: Hypertension: The Continuing Challenge, Scientific Exhibit, Meeting of AAFP, Boston, Mass., Sept. 20-23, 1976. **4.** Fries, E.D.: The treatment of hypertension: Why, when and how, in Hypertension Manual (Laragh, J.H., ed.), New York, Dun-Donnelley, 1974, p. 751. **5.** Tarazi, R.C.: Modern concepts in diuretic therapy, Postgrad. Med. 56:37, 1974.

subaortic stenosis with a resting pressure gradient. In the latter group early systolic closure was a sensitive indicator of the resting intraventricular pressure gradient before operation. After operation, in every instance the early systolic closure disappeared with elimination of the resting gradient. Early systolic closure of the aortic valve occurred later in the cardiac cycle in the patients with idiopathic hypertrophic subaortic stenosis than in those with discrete subaortic stenosis. This is a reliable echocardiographic finding and useful to distinguish between idiopathic hypertrophic and discrete subaortic stenosis.

830 Determinants of the Amplitude of the Aortic Component of the Second Heart Sound in Aortic Stenosis

HANI N. SABBAH, FAREED KHAJA, DANIEL T. ANBE, GORDON M. FOLGER, Jr. and PAUL D. STEIN

Pliable, thin and stretchable valve leaflets present in normal or congenitally stenotic but undamaged aortic valves are shown to be capable of vibrating after closure and of producing a second aortic sound of normal intensity. In contrast, rigid, thickened and unstretchable valve leaflets found in calcific aortic stenosis lack the ability to vibrate after closure and produce a diminished second sound. These experimental in vitro and in vivo investigations are consistent with the concept that the second heart sound is produced by diastolic vibration of the closed aortic cusps. This mechanism explains the paradoxical difference of behavior of the second heart sound in calcific aortic stenosis where the second aortic sound is diminished and congenital noncalcific aortic stenosis where it is not. Although additional variables, still largely unexplained, are likely to affect the amplitude of the second heart sound, as discussed in this paper, the increased stiffness of the aortic valve is the predominant cause of the diminished second sound in calcific aortic stenosis.

836 Assessment of Mitral Valve E Point-Septal Separation as an Index of Left Ventricular Performance in Patients With Acute and Previous Myocardial Infarction

WILBUR LEW, HARMUT HENNING, HEINZ SCHELBERT and JOEL S. KARLINER

These results in 60 patients show E point-septal separation (measured as the minimal distance between the E point of the anterior mitral valve leaflet to a line tangent to the most posterior excursion of the interventricular septum within the same cardiac cycle) is a new, useful, simple echocardiographic index of left ventricular function requiring only visualization of the mitral valve and interventricular septum, which can be achieved in virtually all patients. An abnormal E point-septal separation (more than 5.5 mm) can identify depressed left ventricular function in patients with acute myocardial infarction and chronic ischemic heart disease. However, since 28 percent of the group with a normal E point-septal separation had a depressed radionuclide ejection fraction, a normal value does not exclude the presence of abnormal left ventricular function in such patients.

846 Significance of Changes in R Wave Amplitude During Treadmill Stress Testing: Angiographic Correlation

PETER E. BONORIS, PAUL S. GREENBERG, MARK J. CASTELLANET and MYRVIN H. ELLESTAD

This retrospective review of coronary angiograms and treadmill stress tests in 89 patients showed 91 percent of those with normal coronary arteries had a decrease in R wave amplitude in their immediate postexercise electrocardiogram; only 3 patients (2 of whom showed evidence of segmental abnormalities in their left ventricular angiogram indicating left ventricular dysfunction) showed an increase. Of the patients with angiographically proved coronary artery disease, 59 percent (primarily those with two or three vessel disease) had an increase in R wave amplitude; 41 percent (primarily those with one or two vessel disease) showed a decrease in R amplitude. These results suggest that a decrease in R wave amplitude during exercise stress testing implies normal or only minimally impaired left ventricular function and is usually seen in subjects with normal coronary arteries or mild to moderate coronary artery disease. An increase in R wave amplitude during stress testing suggests significantly impaired left ventricular function with elevated ventricular systolic and diastolic volumes and pressures and is more likely associated with severe coronary arterial narrowing.

852 Correlative Studies of Serum Digitalis Levels and the Arrhythmias of Digitalis Intoxication

WILLIAM SHAPIRO

Although these data and other representative studies on consecutive normokalemic patients with high serum glycoside levels support the general observation that digitalis intoxication is statistically more likely in normokalemic digitalized patients with serum glycoside levels above 2 ng/ml, it is difficult to define any arbitrary clinically useful glycoside level that accurately distinguishes toxicity. Serial studies in 10 hypokalemic patients revealed an inconsistent relation between the pressure of arrhythmia and serum digoxin level. Although the serum glycoside level has sharp limitations as an independent diagnostic indicator of toxicity, it can be used, with the appropriate correlative facts, as an accurate mirror of myocardial threshold to arrhythmias associated with glycoside toxicity and in regulating the management of digitalized patients.

Continued on page A17

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Precautions: Tolerance and cross tolerance to other nitrates may occur.

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CONTENTS

860 Fascicular Conduction Disturbances After Coronary Bypass Surgery

STEVEN M. ZELDIS, JOEL MORGANROTH, LEONARD N. HOROWITZ, ERIC L. MICHELSON, MARK E. JOSEPHSON, EUGENE C. LOZNER, HORACE MacVAUGH, III and JOHN A. KASTOR

New fascicular conduction disturbances developing in 20 percent of 200 patients undergoing coronary artery bypass graft surgery included isolated right bundle branch block (6 percent), left anterior hemiblock (6 percent), left bundle branch block (3 percent) and complete heart block (1 percent). Isolated right bundle branch block was usually transient and unassociated with further complications, but patients with transient or persistent left bundle branch block or left anterior hemiblock, or both, showed increased late mortality and late morbidity, including late myocardial infarction, probably because of their more extensive ischemic heart disease. The appearance of such new left fascicular conduction defects warrants close follow-up after coronary artery bypass surgery.

EXPERIMENTAL STUDIES

865 Hemodynamic Significance of the Length of a Coronary Arterial Narrowing

ROBERT L. FELDMAN, WILMER W. NICHOLS, CARL J. PEPINE and C. RICHARD CONTI

Although these investigators recommend caution be exercised in extrapolating their animal data to predict possible hemodynamic consequences of coronary artery disease in man, they conclude, nevertheless, on the basis of their studies in 14 dogs, that the length of a coronary arterial narrowing is an important consideration in determining the hemodynamic significance of a given coronary obstruction. In a clinical setting the significance of a narrowing is influenced not only by its length, but also by potential compensatory mechanisms including collateral vessels. Short 40 to 60 percent narrowings had no significant resting hemodynamic influence, but increasing their length to 10 and 15 mm consistently and significantly reduced pressure gradients and flow. Reactive hyperemic coronary blood flow decreased progressively as narrowings were lengthened. The net effect of 15 mm long narrowings of 40 to 60 percent on resting and reactive hyperemic flows was similar to that of short 90 percent narrowings.

872 Effects of Lidocaine on Hypoxic and Ischemic Cardiac Cells

RALPH LAZZARA, NABIL EL-SHERIF, RONALD R. HOPE and BENJAMIN J. SCHERLAG

In an effort to clarify the antiarrhythmic effects of lidocaine, canine cardiac cells severely ischemic or hypoxic were exposed to lidocaine in vitro while intracell and extracell potentials were recorded. Lidocaine in therapeutic concentrations invariably abolished propagated action potentials in severely affected cells and modestly reduced membrane responsiveness in nearly normal cells. Concomitantly, abnormal spontaneous beats disappeared with exposure to lidocaine. Lidocaine greatly prolonged the recovery of responsiveness of abnormal cells. These and other data discussed in this article indicate that lidocaine abolished abnormal spontaneous beats by extinguishing very slow conduction arising from depressed fast channels. However, the specific factors and mechanisms by which the fast channel may be depressed, independent of the level of membrane potential, remain to be elucidated.

880 Effect of Propranolol on Mitochondrial Morphology During Acute Myocardial Ischemia

ROBERT A. KLONER, MICHAEL C. FISHBEIN, EUGENE BRAUNWALD and PETER R. MAROKO

These observations on the effects of propranolol on the rat myocardium during the early phase of acute myocardial ischemia show that this drug decreased myocardial cell injury and microvascular damage but exerted an even more profound effect in reducing mitochondrial swelling. There were no significant differences in incidence or degree of nuclear glycogen, sarcoplasmic reticular and myofilament changes in the injured myocardial cells of the rats receiving propranolol and those not receiving it. These results indicate that propranolol's effect was maximal in protecting the mitochondria and suggest mitochondrial salvage plays a major role in the ability of propranolol to protect the ischemic myocardium. Although the mechanism by which propranolol preferentially preserves mitochondrial integrity is unclear, it may possibly be related to its ability to reduce myocardial oxygen demand.

METHODS

887 Techniques for Right and Left Ventricular Endomyocardial Biopsy

JAY W. MASON

This paper offers a detailed description of the optimal methods, based on safety, ease and tissue yield, for nonsurgical biopsy of the beating human heart. Right ventricular endomyocardial biopsy using percutaneous right internal jugular approach proved a safe, easily performed technique in more than 1,300 procedures. The major complications associated with right ventricular biopsy were cardiac perforation and tamponade, which occurred

Continued on page A19

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four times. Other complications relate to internal jugular vein puncture. Retrograde left ventricular endomyocardial biopsy is the safest and most reliable alternative to transjugular right ventricular biopsy. Meticulous attention to detail, as spelled out in this article, is necessary for the safety and success of both techniques.

893 Retrograde Left Ventricular Catheterization in Patients With an Aortic Valve Prosthesis

DENNIS L. KARSH, STEPHEN P. MICHAELSON, RENE A. LANGOU, LAWRENCE S. COHEN and STEVEN WOLFSON

Retrograde left ventricular catheterization was successfully performed without complications in 27 consecutive patients with an aortic valve prosthesis, including 3 patients with active endocarditis or recent embolization. Pressure tracings and cineangiographic films suggested only minor interference with valve poppet movement induced by the catheter traversing the valve. The place and uses of this technique will have to be clarified since the magnitude of the regurgitant aortic flow in many patients with aortic valve dysfunction due to a paraprosthetic leak may be sufficient to allow filling of the left ventricle with contrast medium on aortography and assessment of left ventricular and mitral valve function in this manner. This technique is particularly useful in laboratories unable or unwilling to perform or risk transseptal catheterization.

897 Assessment of Cardiac Performance With Quantitative Radionuclide Angiocardiography: Right Ventricular Ejection Fraction With Reference to Findings in Chronic Obstructive Pulmonary Disease

HARVEY J. BERGER, RICHARD A. MATTHAY, JACOB LOKE, ROBERT C. MARSHALL, ALEXANDER GOTTSCHALK and BARRY L. ZARET

Quantitative first pass radionuclide angiocardiographic methods, originally shown to provide relatively simple means for evaluating ejection fraction, ejection rate and regional wall motion from the high frequency components of time-activity curves derived from the left ventricle, have been adapted in this study to provide right as well as left ventricular performance concomitantly from the same examination. In 50 normal adults right ventricular ejection fraction averaged 55 percent, was reproducible with minimal inter- and intraobserver variability, and was sensitive to changes in the inotropic state induced with isoproterenol. In 36 patients with chronic obstructive pulmonary disease, right ventricular ejection fraction ranged from 19 to 71 percent. All 10 patients with cor pulmonale and 9 additional subjects had an abnormal right ventricular ejection fraction. There was no relation between abnormalities in right and left ventricular ejection fraction. This technique is equally applicable to the study of patients with ischemic heart disease, primary myocardial disease or congenital abnormalities predominantly affecting the right ventricle.

PEDIATRIC CARDIOLOGY

906 Primary Repair of Complete Atrioventricular Canal in Patients Less Than 2 Years Old

THOMAS J. BERGER, JOHN W. KIRKLIN, EUGENE H. BLACKSTONE, ALBERT D. PACIFICO and NICHOLAS T. KOUCHOUKOS

This analysis of 27 consecutive patients less than 2 years of age undergoing primary intracardiac repair of complete atrioventricular (A-V) canal attributes improved results in the 16 patients operated upon since January 1, 1975 primarily to improved ability to construct "mitral" and "tricuspid valves" from the common A-V valve. Fourteen of the 16 hospital survivors are alive and well 5 to 60 months after operation. These results and the natural history of patients with this malformation reinforce the present policy of performing elective intracardiac repair before age 2 years and primary repair rather than pulmonary arterial banding when operation is required in the early months of life. Patients with unrepaired complete A-V canal often have severe pulmonary vascular disease by age 2 years and only about 20 percent of such patients live to age 5.

914 Differentiation of Functional and Structural Pulmonary Atresia: Role of Aortography

ROBERT M. FREEDOM, GORDON CULHAM, FREDERICK MOES, PETER M. OLLEY and RICHARD D. ROWE

Among certain critically ill neonates with severe tricuspid regurgitation, selective right ventriculography may not distinguish between patients with associated functional and those with structural pulmonary atresia. In 33 such neonates retrograde aortography, in the presence of a patent ductus arteriosus, provided excellent visualization of the pulmonary root and valve. Pulmonary regurgitation across the valve was observed during the late phase of right ventricular systole or early diastole in the patients with functional pulmonary atresia. The pulmonary infundibulum in these patients appeared widely dilated and patulous, and the pulmonary valve ring was normal or dilated. Aortography using this method may obviate unnecessary exploratory thoracotomy in most patients with functional pulmonary atresia.

Continued on page A21



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921 Hypertensive Pulmonary Vascular Disease in *d*-Transposition of the Great Arteries

WILLIAM D. EDWARDS and JESSE E. EDWARDS

This study of 35 cases with classic complete transposition (*d*-transposition) of the great arteries revealed that in 15 patients, aged 12 to 30 months, the pulmonary arterial plexiform lesion characteristic of chronic high levels of pulmonary arterial pressure was observed in 6 of 12 patients with an intact ventricular septum and a closed ductus arteriosus and in 1 of 4 patients with an associated ventricular septal defect. Unlike other reports showing grade 3 or 4 lesions in the first year of life, this lesion was not found in subjects younger than 12 months, possibly because most of these younger subjects in this series were less than 6 months old. Although one cannot disprove the concept that the pulmonary arterial vessels are peculiarly different in *d*-transposition from those in other conditions, the structural changes must be viewed as a result rather than a cause of pulmonary hypertension. The origin of the pulmonary hypertension in *d*-transposition with intact ventricular septum remains an unexplained fundamental question.

REPORTS ON THERAPY

925 Comparative Hemodynamic Effects of Intravenous Nitroprusside and Oral Prazosin in Refractory Heart Failure

JAWAHAR MEHTA, MARIE IACONA, ROBERT L. FELDMAN, CARL J. PEPINE and C. RICHARD CONTI

Prazosin, a quinazoline derivative used orally in the therapy of hypertension, has both arterial resistance and venous capacitance vessel dilator effects. Comparison of its hemodynamic effects given orally with intravenous nitroprusside in 10 patients with refractory heart failure shows that the effects of prazosin, attributable to its vasodilator properties, are qualitatively similar to but slightly less potent quantitatively than those observed with intravenous nitroprusside. The hemodynamic changes appeared 1 hour after the administration of a single dose of oral prazosin and persisted for 6 hours. No serious untoward side effects were observed with either drug. All 10 patients reported noticeable alleviation of symptoms of low cardiac output such as fatigue and weakness and of pulmonary congestion such as orthopnea and dyspnea. These hemodynamic data suggest prazosin has beneficial effects in certain patients with heart failure who respond to intravenous nitroprusside infusion, namely, those with low stroke volume and high left ventricular filling pressure. For clinical safety, the dose should be small initially (2 mg twice daily) and then increased to 4 or 5 mg twice daily.

931 Effect of Sublingual Nitroglycerin in Emergency Treatment of Severe Pulmonary Edema

WULF-DIRK BUSSMANN and DOROTHEE SCHUPP

Hemodynamic studies in 7 patients and clinical responses in 15 patients indicate the beneficial effects of sublingual administration of nitroglycerin in the emergency treatment of classic pulmonary edema. After the use of nitroglycerin in these patients, elevated left ventricular filling pressure decreased and cardiac output increased within 5 minutes, producing immediate clinical improvement. In one patient with recent myocardial infarction, left ventricular filling pressure decreased from 50 to 27 mm Hg within 5 minutes, and orthopnea and pulmonary rales disappeared rapidly. In patients with hypotension, administration of nitroglycerin may be detrimental because reduction of coronary perfusion pressure may enhance myocardial ischemia. Although nitroglycerin can effect immediate clinical improvement by decreasing left ventricular filling pressure within 5 minutes of its administration, nitroglycerin therapy should not replace the use of morphine, diuretics and digitalis as the standard treatment of pulmonary edema.

937 Left Ventricular Dynamics During Long-Term Digoxin Treatment in Patients With Stable Coronary Artery Disease

JAY H. KLEIMAN, NEIL B. INGELS, GEORGE DAUGHTERS II, EDWARD B. STINSON, EDWIN L. ALDERMAN and ROBERT H. GOLDMAN

Assessing left ventricular function with computer-assisted fluoroscopic analysis of recordings of the motion of surgically implanted mid wall markers that outline the left ventricular cavity, this study of 10 patients with stable coronary artery disease without clinical congestive heart failure at least 3 months after coronary artery bypass confirms that both intravenous digoxin given acutely and long-term oral digoxin administration augment ventricular function as shown by increases in ejection fraction and velocity of circumferential fiber shortening. This potential clinical benefit of digitalis treatment persists undiminished for at least 4 weeks. End-diastolic volume and cardiac output did not change significantly.

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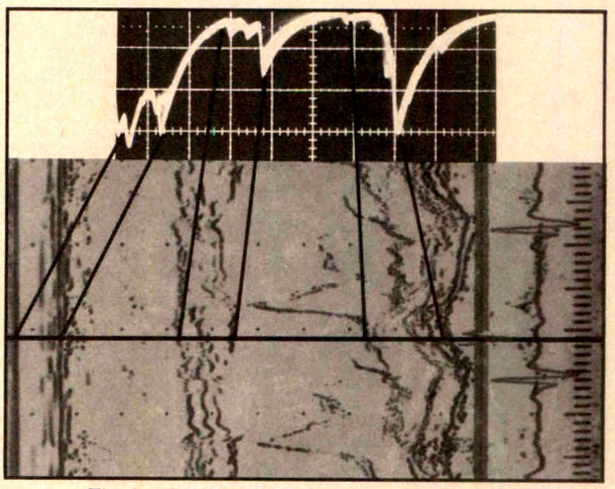
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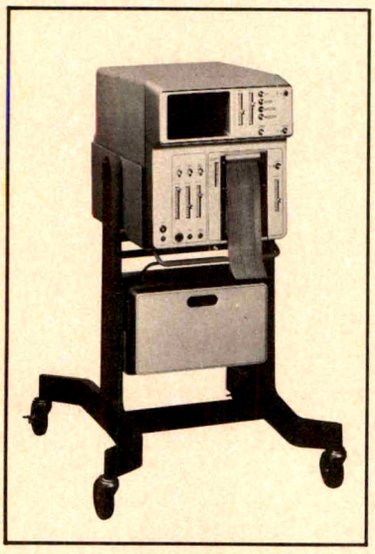


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REVIEWS

943 Exercise Testing for Detection of Myocardial Ischemia in Patients With Abnormal Electrocardiograms at Rest

BORYS SURAWICZ and SATOSHI SAITO

This review discusses briefly the electrophysiologic mechanisms believed responsible for the ventricular repolarization changes during the stress test and summarizes the reported studies of electrocardiographic stress testing in subjects with an abnormal electrocardiogram at rest. The electrocardiographic manifestations of ischemia may be masked by intraventricular conduction defects, quinidine, phenothiazines and propranolol and simulated or exaggerated by digitalis, diuretics, methyldopa, diazepam, left ventricular hypertrophy pattern and other abnormalities discussed in this review. The term "anamnestic response" is proposed to characterize the transient reappearance of the pattern of acute injury of the initial stage of myocardial infarction during tachycardia after exercise in patients with healed myocardial infarction. The electrophysiologic mechanism of the exercise-induced "anamnestic response" remains obscure.

DIAGNOSTIC SHELF

952 Musical Murmurs: An Echo-Phonocardiographic Study

KALYANASUNDARAM VENKATARAMAN, ROBERT SIEGEL, SUN JUNE KIM and JOHN W. ALLEN

Muscial murmurs constitute a unique auscultatory sign in patients with a variety of cardiac abnormalities. Using simultaneous recording of echocardiograms and phonocardiograms to study five patients with musical murmurs, these investigators demonstrated regular valve leaflet flutter (aortic, mitral or tricuspid) at a frequency identical to that of the simultaneously recorded musical murmur. They hypothesized that the primary source of murmur production is an intrinsic leaflet abnormality that allows leaflet vibration. In the presence of the leaflet abnormality, the proper hemodynamic milieu will provide the initiating flow pattern that leads to leaflet flutter and murmur generation. This demonstration establishes echocardiography as a valuable noninvasive tool for localizing the origin of both systolic and diastolic musical murmurs from various valves.

CASE REPORTS

956 Familial Study of Hypertrophic Cardiomyopathy and Congenital Aortic Valve Disease

ÖZGEN FEIZI, GEOFFREY FARRER-BROWN and RICHARD EMANUEL

This report presents the unusual, ultimately fatal case of a 48 year old woman with histologically documented hypertrophic cardiomyopathy coexisting with a congenitally bicuspid aortic valve and an aorta with an abnormal "higgledy-piggledy" histologic pattern consisting of disordered arrangement of the smooth muscle and elastic tissue. Subsequently clinical and echocardiographic studies of 10 asymptomatic relatives from four generations of her family revealed hypertrophic cardiomyopathy and bicuspid aortic valve may coexist and be inherited as a dominant characteristic with variable manifestations.

EDITORIALS

965 Myocardial Biopsy: A Useful Diagnostic Procedure or Only a Research Tool?

VICTOR J. FERRANS and WILLIAM C. ROBERTS

SPECIAL DEPARTMENTS

968 Books Received

970 American College of Cardiology News

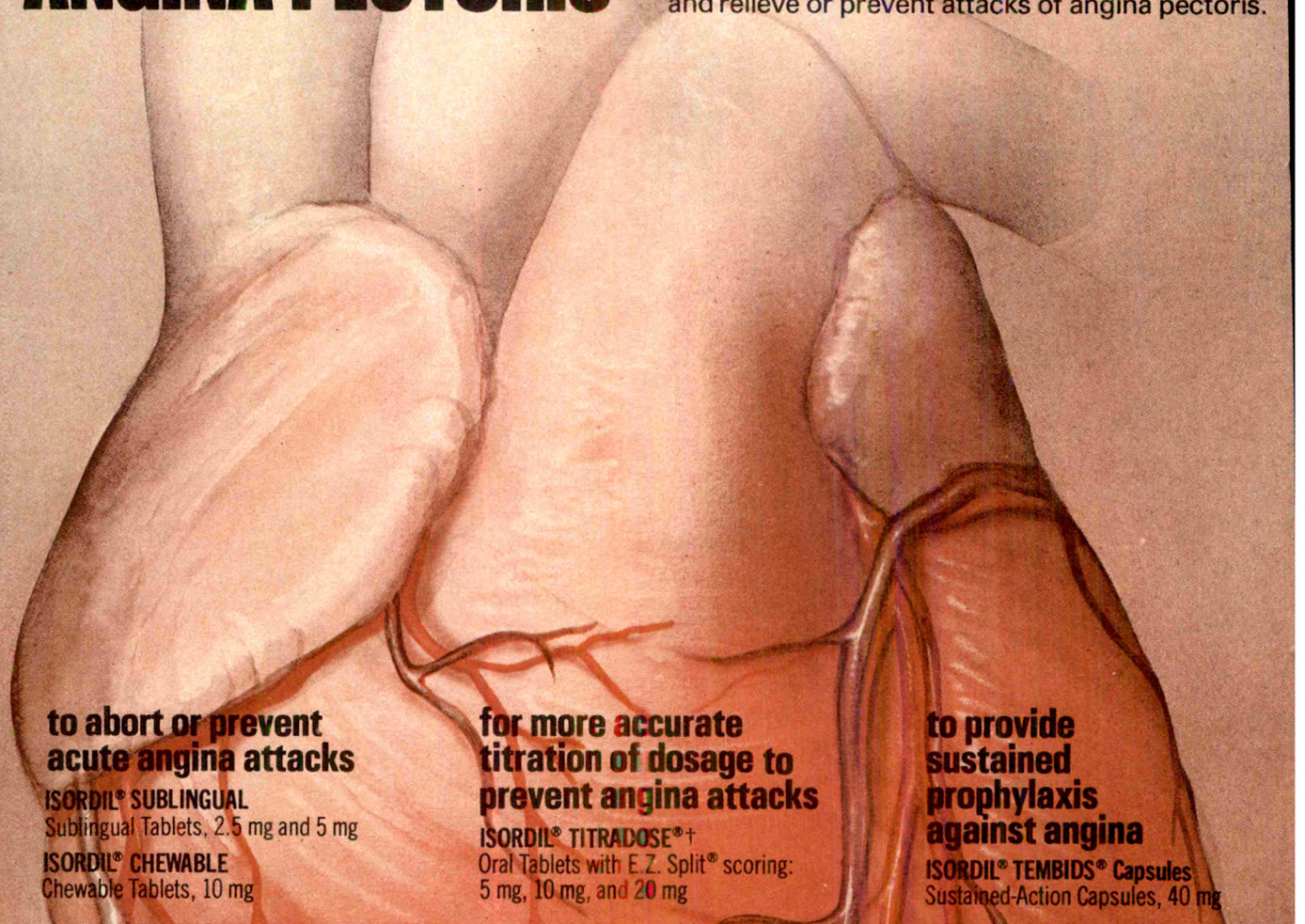
CORRECTION

The authors regret two errors that appeared in their article on "Internally Recorded Systolic Time Intervals in Hypertrophic Subaortic Stenosis" in the November 1977 issue of the Journal (Stefadouros MA, Canedo MI, Karayannis E, et al: Am J Cardiol 40:700–706, 1977). On page 702, right column, line 9, the sentence should read: "Measurements of these intervals were made to the nearest 0.5 mm, which was equivalent to 2.5, 3.3, 5.0, 6.7 and 10 msec for a paper speed of 200, 150, 100, 75 and 50 mm/sec, respectively." On page 703, left column, line 7, the sentence should read: "This relation yielded a correlation coefficient of $r = 0.87$ ($P < 0.001$) for the 21 data points from the 15 untreated patients."

ISORDIL®
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The established use of Isordil in the management of angina pectoris for more than two decades has often been ascribed only to the vasodilatation it produces in the coronary arteries. Recent investigations, however, suggest that an even more important effect of this agent is to dilate peripheral arteries and veins. Arterial dilatation lowers impedance to left ventricular ejection, reducing afterload. Venous dilatation leads to venous pooling and a fall in right and left ventricular filling pressure, thus reducing preload.

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Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

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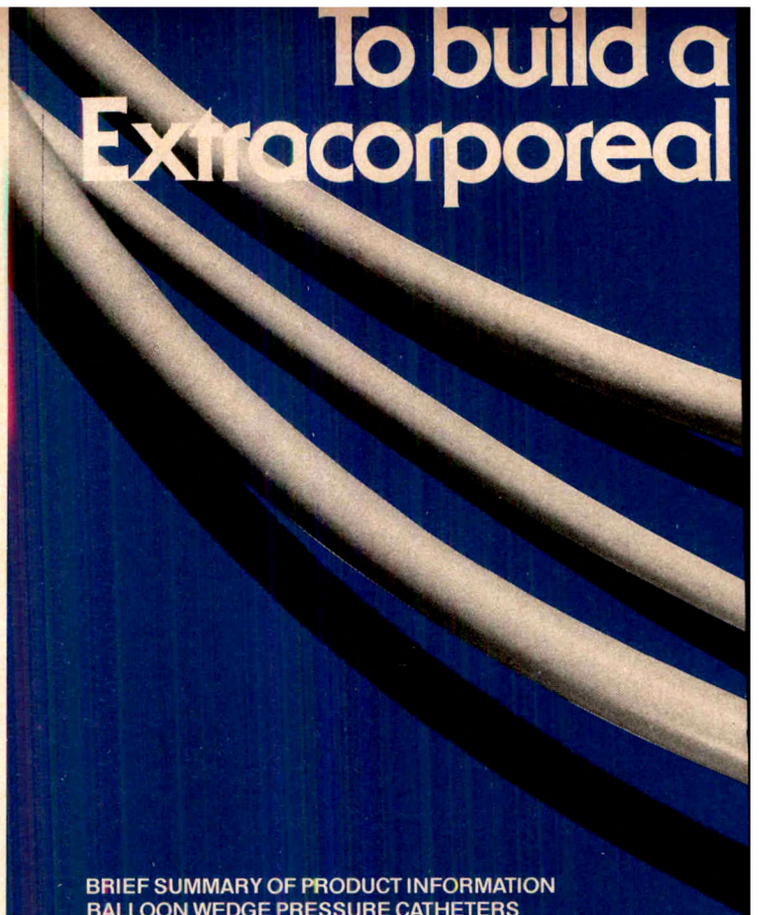
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BRIEF SUMMARY OF PRODUCT INFORMATION

BALLOON WEDGE PRESSURE CATHETERS

Indications: For sampling blood for oxygen levels and measuring pressures in the right heart, including central venous, right ventricular, pulmonary artery, and pulmonary artery wedge pressure. Also indicated in anatomical cardiac defect cases to sample blood and measure pressures in any chambers that can be entered from the right heart. **Warning:** Pulmonary artery perforation, thrombosis, segmental pulmonary infarction, transient obstruction of the pulmonary outflow by the inflated balloon, balloon rupture without serious sequelae, premature ventricular contractions, and knotting of the catheter have been reported as complications of the use of balloon catheters. Balloon rupture with possible latex embolus is a potential complication in the use of balloon catheters. **Precaution:** In pressure monitoring at bedside when catheter has been introduced in an antecubital vein, patient's arm should be immobilized to reduce the possibility of catheter advancement due to arm motion.

BERMAN ANGIOGRAPHIC CATHETER

Indications: For use in right-heart catheterization for cardiac angiography, pulmonary angiography, and measurement of right-heart and pulmonary artery pressures. It can be used to inject radiopaque media and measure pressures in any chambers and vessels that can be entered from the right heart. **Warnings:** Angiograms should be done with balloon inflated to minimize myocardial staining. When injecting radiopaque media, do not exceed stated maximum flow rate and pressure. Transient obstruction of the pulmonary outflow tract, balloon rupture without serious sequelae, premature ventricular contractions, and knotting of catheters are reported complications of the use of balloon catheters. Balloon rupture with possible latex embolus is a potential complication in the use of balloon catheters. **Precaution:** Manipulate catheter carefully and gently to avoid kinking or knotting.

BIPOLAR TEMPORARY PACING W/STYLET AND BALLOON TEMPORARY PACING CATHETERS

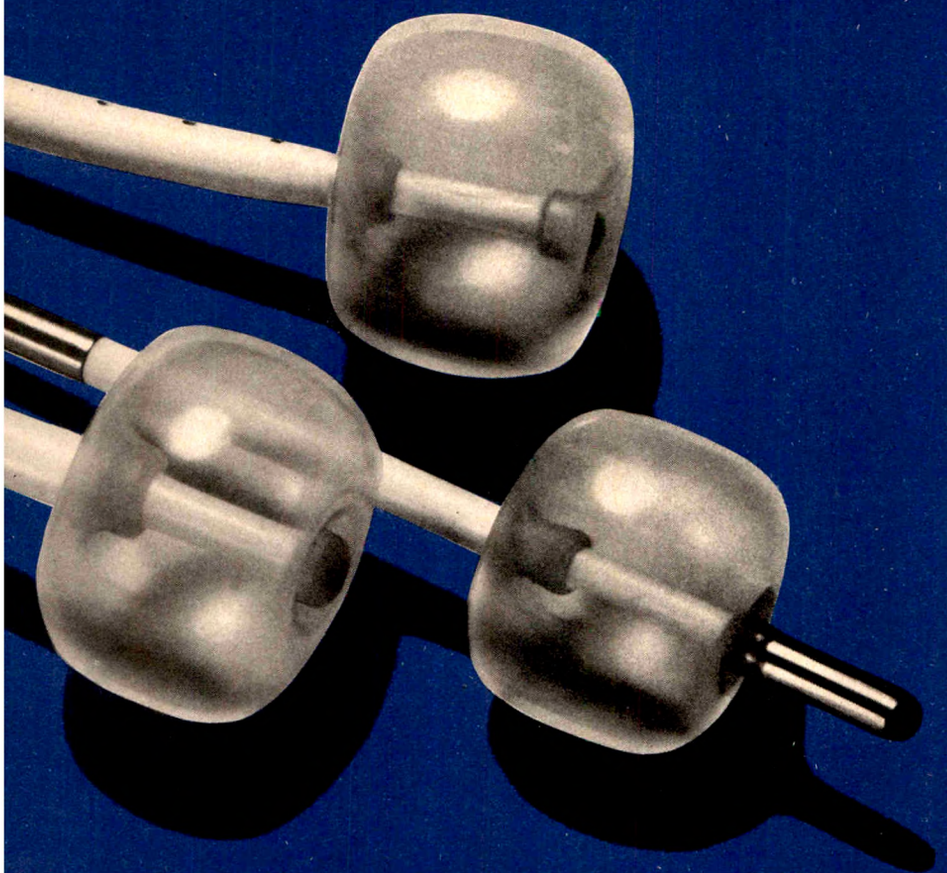
Indications: For temporary transvenous cardiac pacing when impulse formation or conduction is impaired. **Warnings:** Myocardial perforation, fibrillation and arrhythmia, pulmonary embolism, thrombus formation, and infection are general complications of transvenous pacing. Balloon rupture with possible latex embolus, vessel perforation, and intimal disruption are potential complications of use of balloon temporary pacing catheters. With the transbrachial approach, malpositioning and perforation occur more frequently due to arm movement. Pneumothorax, air embolism, and puncture of the subclavian artery have been reported with the subclavian approach. **Precautions:** Avoid kinking or bending catheter to prevent damage to internal wires or occlusion of inflation lumen (in balloon pacing catheter). Maintain insertion site with regular meticulous redressing performed with aseptic technique. Remove stylet from Bipolar Pacing Catheter after it is in position because leaving stylet *in situ* increases the potential for perforation.

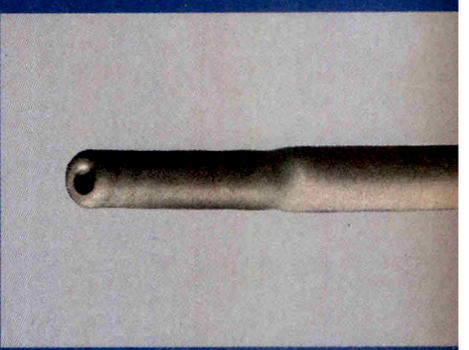
FOR BALLOON CATHETER USE, IN GENERAL

General Warnings: Carbon dioxide must be used to inflate balloon if there is a possibility that balloon rupture would result in air embolism in the left heart or systemic circulation. Do not inflate balloon beyond stated maximum inflation capacity. Exercise care when passing catheters in patients with left bundle-branch block because right bundle-branch block induced by traumatic catheter passage could result in complete heart block and asystole. **General Precautions:** Do not use liquids as balloon-inflation media. Pass catheter with continuous cardiographic monitoring and fluoroscopic guidance, and confirm final tip position by X-ray. Deflate balloon prior to withdrawing catheter to avoid possible valve damage. Use aseptic technique throughout procedure. All catheters are for single use only. Do not resterilize or reuse. Federal law (U.S.A.) restricts these devices to sale by or on the order of a physician. **Contraindication:** Not for use except as indicated.

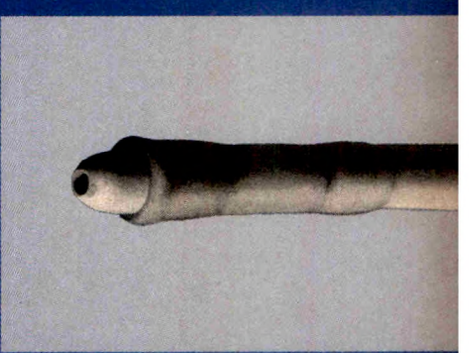
For complete use information, see the package insert.

better cardiac catheter, starts with a built-in tip.





The Extracorporeal built-in tip, balloon deflated.



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As you can see, the Extracorporeal tip is smooth, tapered, unruffled, suture free, no wider than the catheter itself. The benefits are built-in:

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- **The tip is suture-free,** eliminating clotting caused by the sutures' irregular surface.

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- **Inflation is more convenient** because every Extracorporeal balloon catheter is packaged with an appropriately sized syringe.
- **Pure platinum electrodes for better electrical characteristics.** Blood may alter the conductivity properties of stainless steel and cause inferior readings. That's why our balloon pacing catheters employ only inert platinum for electrodes.
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- **More sizes available.** Especially in Berman angiographic and wedge pressure models. And we can supply custom catheters, too.
- **Even our package works hard for you.** Each catheter comes in its own sterile peel-pack that stores easily and has a fold down tab for quick identification.
- **Our new brochure has all the facts.** Just let us know where you are and we'll send you one. Call your Extracorporeal representative, or write or call us toll free: 800-523-1740.

*With one small exception—the Extracorporeal 4F size uses a 4-1/2 size introducer.

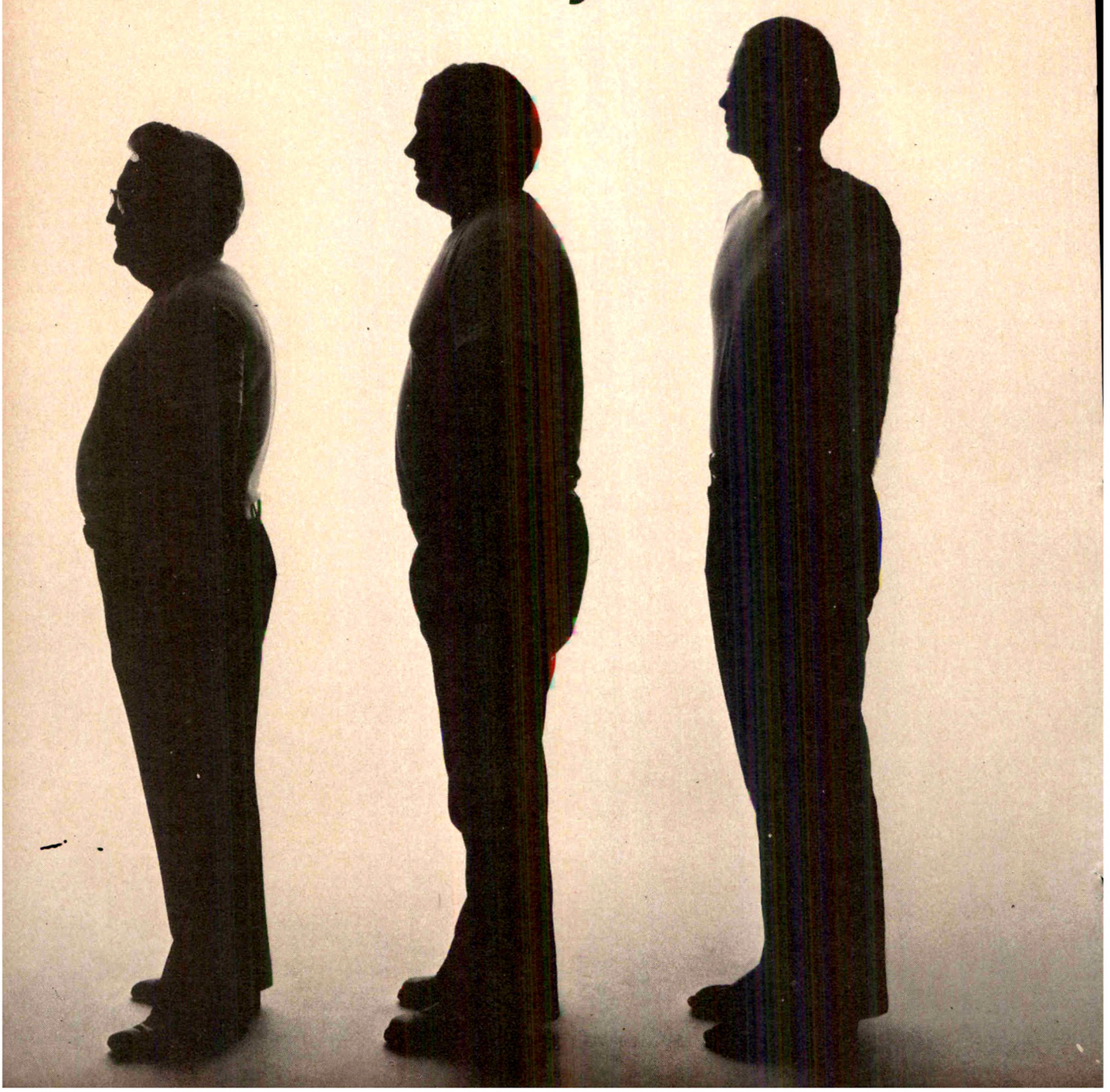
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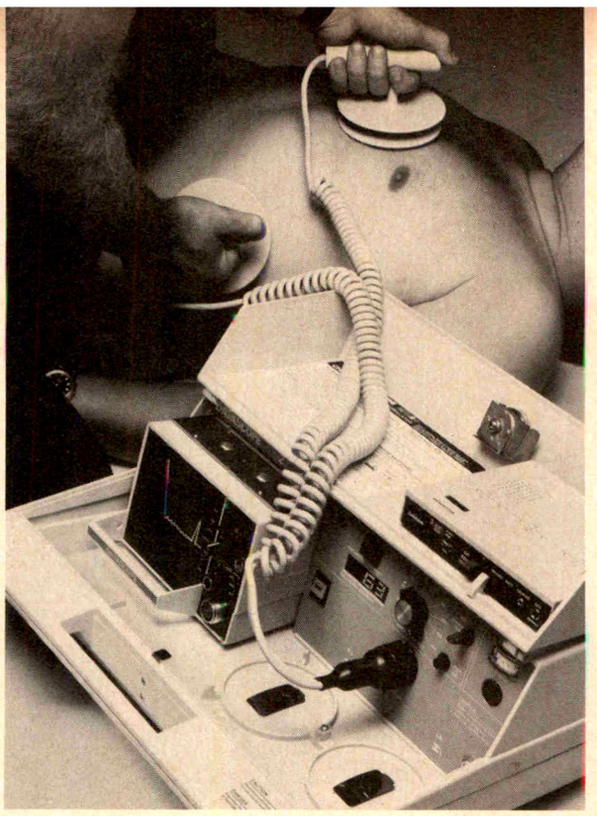
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But the Datascope M/D2J doesn't just de-
r more energy than other defibrillators. It tells
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It is the only defibrillator in the world that
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he subject during de-
illation. (Energy
duces current. But
rent is what produces
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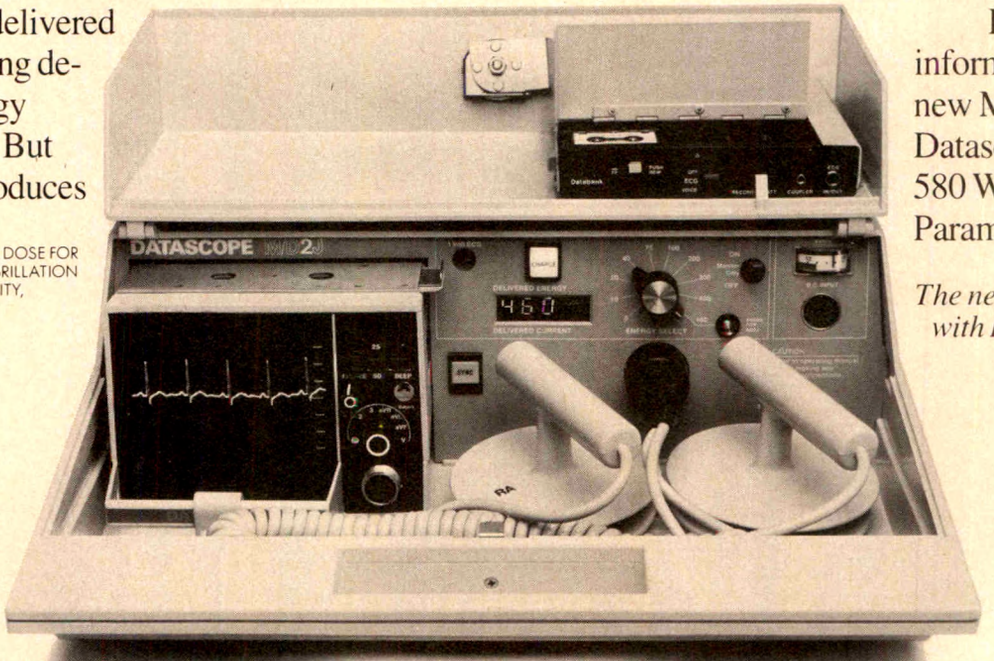
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b.i.d. convenience for many patients

b.i.d. doses can be used for many patients.

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In patients with renal disease, thiazides may precipitate azotemia. Use with caution in patients with severe renal disease or impaired hepatic function.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, see the brief summary of prescribing information.



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containing 500 mg ALDOMET® (Methyldopa, MSD) and 30 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

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For a brief summary of prescribing information, please see following page.

Antihypertensive TABLETS

New ALDORIL® D50
methyldopa 500 mg and hydrochlorothiazide 50 mg

Antihypertensive TABLETS

New ALDORIL® D30
methyldopa 500 mg and hydrochlorothiazide 30 mg

Antihypertensive TABLETS

ALDORIL®-25
methyldopa 250 mg and hydrochlorothiazide 25 mg

Antihypertensive TABLETS

ALDORIL®-15
methyldopa 250 mg and hydrochlorothiazide 15 mg

WARNING

This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be re-evaluated as conditions in each patient warrant.

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see **Warnings**); anuria; routine use in an otherwise healthy pregnant woman with or without mild edema; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs.

Warnings: METHYLDOPA—**It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.**

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within the first three weeks of therapy, sometimes with eosinophilia or abnormalities in one or more liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually within the first two to three months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, reversible reduction of white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Follow patients carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

HYDROCHLOROTHIAZIDE—Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity; read circulars for lithium preparations before use of such concomitant therapy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks.

Methyldopa and thiazides cross the placental barrier and appear in cord blood.

No unusual adverse reactions have been reported in association with the use of methyldopa during pregnancy. Although no obvious teratogenic effects have been reported, the possibility of fetal injury cannot be excluded.

The hazards of thiazides crossing the placental barrier include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in adults. Methyldopa and thiazides appear in breast milk. Patients taking ALDORIL should not nurse.

Precautions: METHYLDOPA—Should be used with caution in patients with history of previous liver disease or dysfunction (see **Warnings**). May interfere with measurement of urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites. Involuntary choreoathetotic movements have been observed in patients with severe bilateral cerebrovascular disease. If such movements occur, stop the drug. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

HYDROCHLOROTHIAZIDE—Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroids or ACTH, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: METHYLDOPA—*Central nervous system:* Sedation, headache, asthenia or weakness; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression. *Cardiovascular:* Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.) *Gastrointestinal:* Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. *Hepatic:* Abnormal liver function tests, jaundice, liver disorders. *Hematologic:* Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells and rheumatoid factor. *Allergic:* Drug-related fever, lupus-like syndrome, myocarditis. *Other:* Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

HYDROCHLOROTHIAZIDE—*Gastrointestinal system:* Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis. *Central nervous system:* Dizziness, vertigo, paresthesias, headache, xanthopsia. *Hematologic:* Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. *Cardiovascular:* Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics). *Hypersensitivity:* Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions. *Other:* Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: Tolerance may occur, usually between the second and third month of therapy. Increasing dosage of either component separately or together frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets ALDORIL®-15, containing 250 mg methyldopa and 15 mg hydrochlorothiazide, bottles of 100 and 1000; Tablets ALDORIL®-25, containing 250 mg methyldopa and 25 mg hydrochlorothiazide, bottles of 100 and 1000; Tablets ALDORIL® D30, containing 500 mg methyldopa and 30 mg hydrochlorothiazide, bottles of 100; Tablets ALDORIL® D50, containing 500 mg methyldopa and 50 mg hydrochlorothiazide, bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486. J7AR08 (021)

MSD
MERCK SHARP & DOHME

Do you really think a mere ocean is going to stop us from giving you great service?

Vitatron, Europe's largest pacemaker manufacturer, is in America.

You probably know all about our lithium-iodine pacemaker, Vitalith,™ with the slightly incredible service life of 12 years.*

You've probably also heard about our absolutely uncompromising dedication to reliability.

But even after knowing all of this, is it possible that you may still be a little reluctant about doing business with a company so far away?

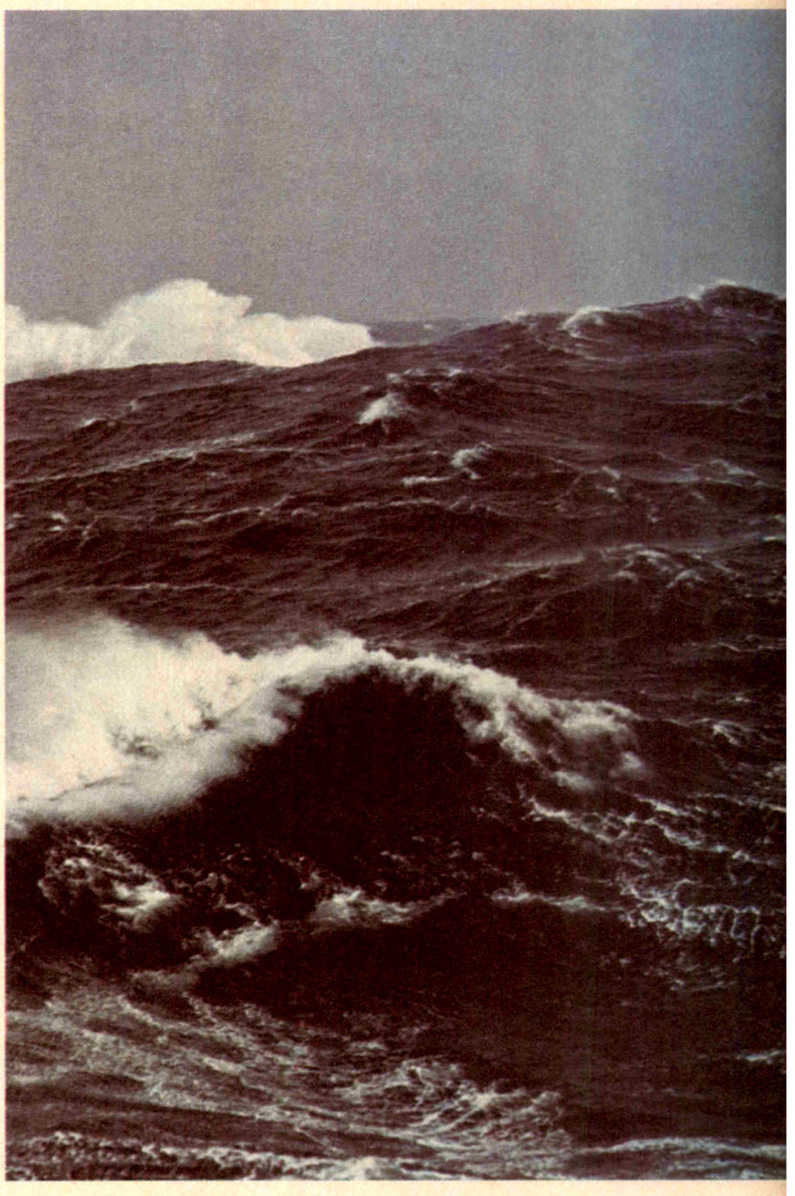
After all, what happens when you need a little service? Or when you just want to consult with someone on a particular pacing application?

What we'd like you to know is, we can give you all of that. And more. We're not really as far away as you think. Our American headquarters is right here in Boston.

It's there to help our customers wherever and whenever they need it. In fact, we guarantee one of our Pacemaker Service Consultants will be available to assist with any problem or answer any question you may have — 24 hours a day, 365 days a year.

So don't worry that we're in Europe. Because if it's one thing we're not about to let happen, it's to have our good service watered down by something as insignificant as an ocean.

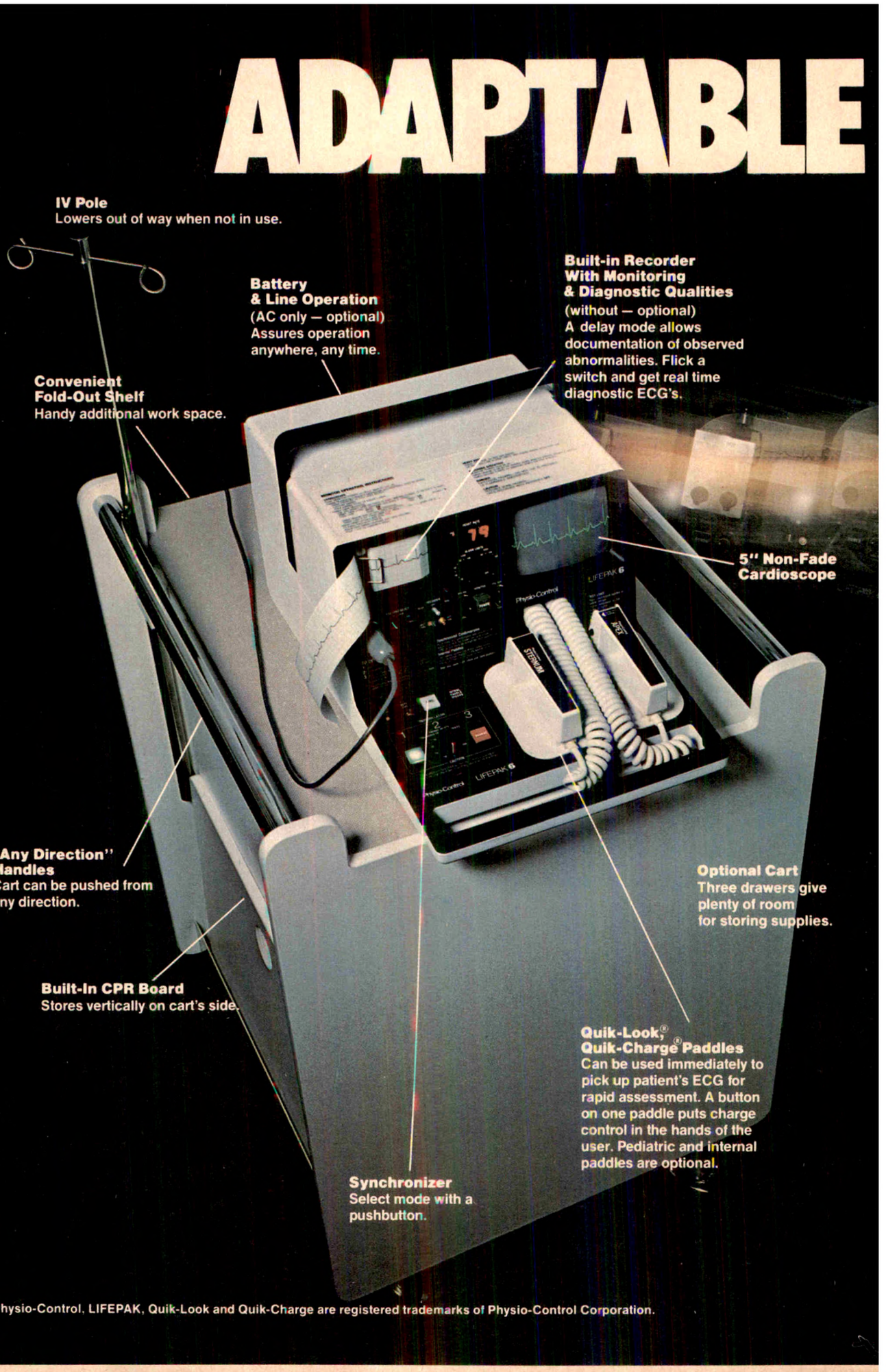
For information, write Vitatron Medical, Inc., One Gateway Center, Newton, MA 02158. Or call (617) 964-1980. In Europe: Vitatron Medical, b.v., P.O. Box 76, NL 6210 Dieren, The Netherlands.



*Over 12 years' service life expected under worst case conditions. 510 ohm load with 1.0 millisecond pulse duration: over 19 years with 0.5 ms duration.

VITATRON MEDICAL

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IV Pole
Lowers out of way when not in use.

Battery & Line Operation
(AC only — optional)
Assures operation anywhere, any time.

Built-in Recorder With Monitoring & Diagnostic Qualities
(without — optional)
A delay mode allows documentation of observed abnormalities. Flick a switch and get real time diagnostic ECG's.

Convenient Fold-Out Shelf
Handy additional work space.

5" Non-Fade Cardioscope

"Any Direction" Handles
Cart can be pushed from any direction.

Optional Cart
Three drawers give plenty of room for storing supplies.

Built-In CPR Board
Stores vertically on cart's side.

Quik-Look,® Quik-Charge® Paddles
Can be used immediately to pick up patient's ECG for rapid assessment. A button on one paddle puts charge control in the hands of the user. Pediatric and internal paddles are optional.

Synchronizer
Select mode with a pushbutton.

Physio-Control, LIFEPAK, Quik-Look and Quik-Charge are registered trademarks of Physio-Control Corporation.

PORTABLE.



Never before has there been a cardiac care system so small that could do so much.

The new Lifepak®6 Defibrillator/Cardioscope can be used for emergencies, diagnostic ECG's and long-term monitoring. It can even do stress tests if you want.

It features ECG monitor and defibrillator modules that work together or independently — each module has its own internal battery and battery charger plus the capability of line operation. Which means you can order each separately. And only with the features you need.

You can also get a beautiful cart that's specifically designed for cardiac emergencies.

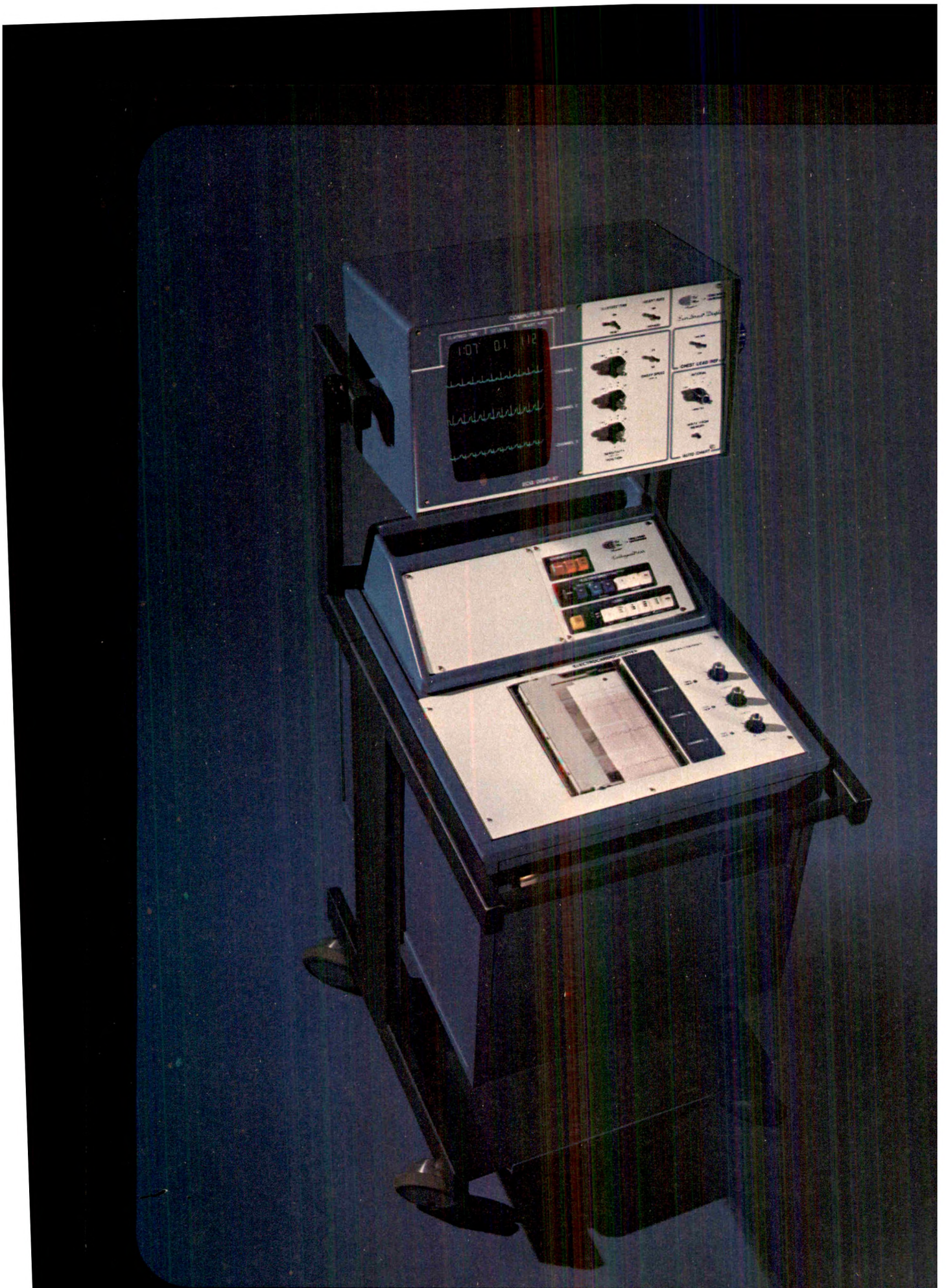
All this is backed up by the most responsive service organization in the country.

Take a minute to compare the features of this portable with *any* other system.

For more details about specific applications of the Lifepak®6, or any additional information about our complete line of equipment, contact Physio-Control Corporation, 11811 Willows Road, Redmond, Washington 98052. Telephone: (206) 883-1181. Cable: PHYSIO-RED. Telex: 32-0166.

THE NEW LIFEPAK®6

Physio-Control®



CARDIOGUARD® 4000 STRESS TEST SYST

we ask questions before any of our instrumentation gets to the drawing board. Because knowing what you need is the most important part of designing what you can use.

Our Cardioguard® 4000 for example. You wanted a system for stress testing and resting ECG your office could use and afford. So the 4000 is compact, mobile, and simple to operate. And with the Exerstress® Display Memory Scope, ST Segment Computer, and our new E-16 Treadmill, you get a complete, automatic 3-channel system for a lot less than you might expect to pay.

The 4000 automatically produces 12-lead ECGs in a letter-size, chart-ready format. With simple push-button controls, you can pre-select any standard lead group, an XYZ lead group, plus your choice of a monitor lead group. And you can change any lead group anytime during the procedure.

The Exerstress Display has a 5-second memory for immediate chart documentation of observed abnormalities. ECG Traces, Elapsed Time, Heart Rate, and the optional ST Level Display all appear on the bright, non-fade, memory scope.

The E-16 Treadmill is our latest. And when coupled with the 4000, the E-16 gives you rugged and reliable performance in speed ranges from 0-10 mph and grades of 0-25 percent, as well as remote control and optional automatic programming.

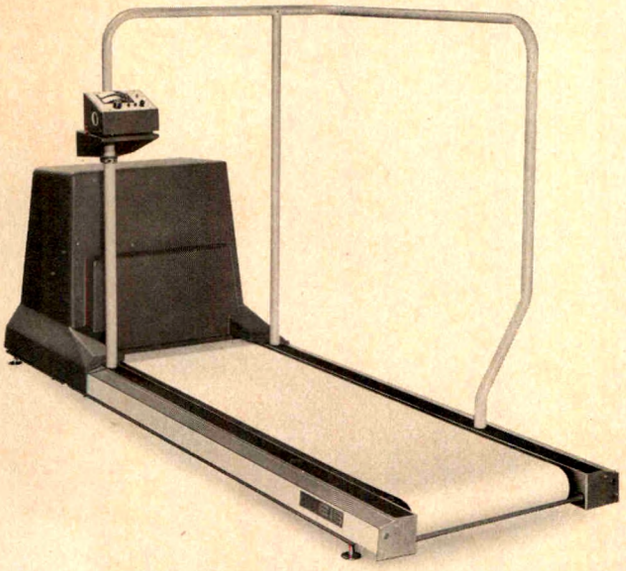
Like all Del Mar Avionics Systems, the 4000 and E-16 are backed by an extensive service and supply network throughout the country. For more information or a demonstration, write Del Mar Avionics, 1601 Alton Avenue, Irvine, California 92714. Or just call any sales/service office listed below.

Together, your ideas and our ideas built the 4000 and E-16. An economical, reliable, yet state-of-the-art approach to exercise stress testing.

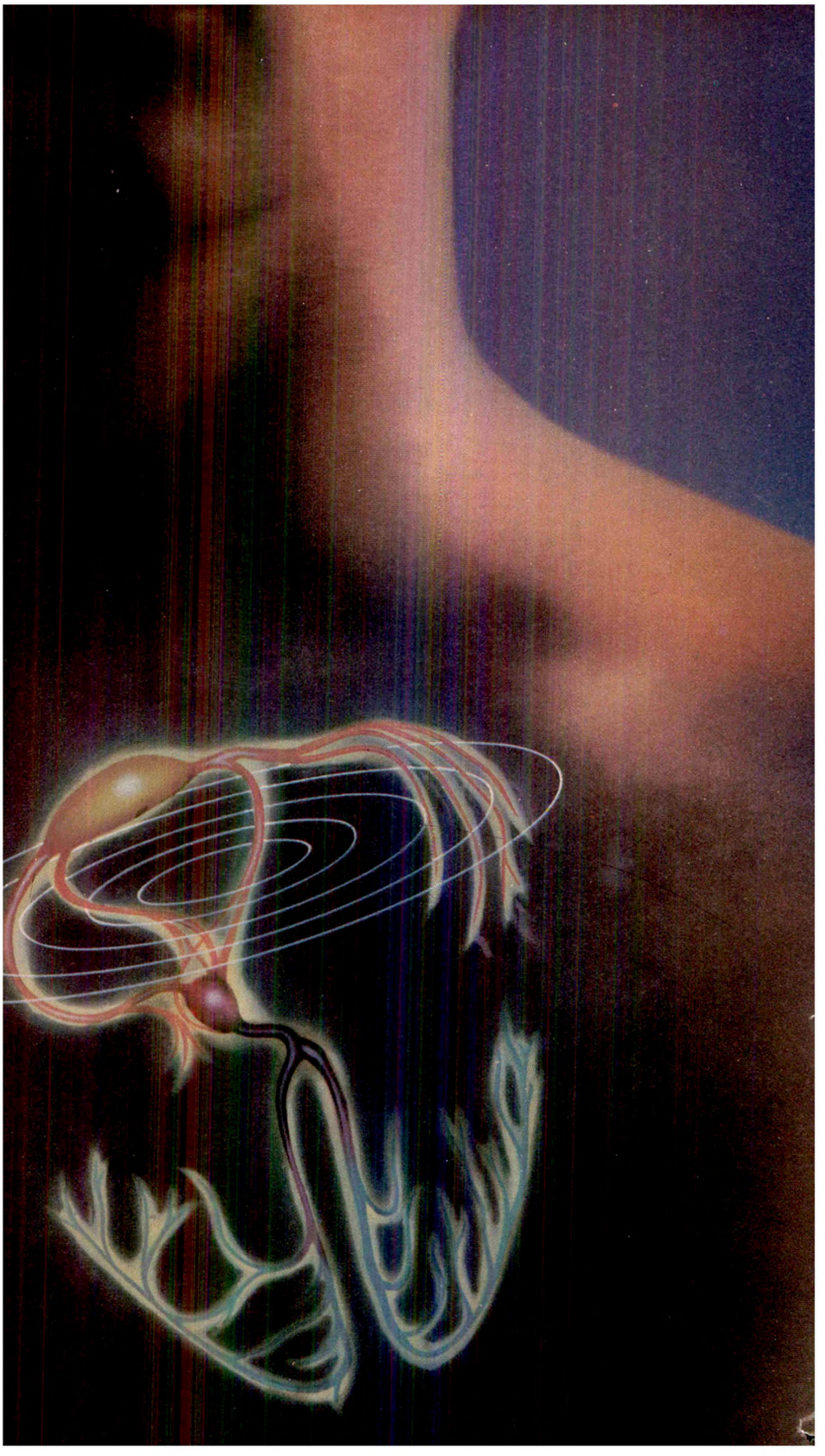
Which is the very reason we ask questions **before we build answers**

ATLANTA (404) 952-0612 • **BALTIMORE** (301) 265-1320 • **BOSTON** (617) 942-0230 • **CHICAGO** (312) 956-6520 • **DENVER** (303) 344-5101
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Model E-16 Treadmill



DEL MAR AVIONICS



Telectronics pacemakers

second only to the heart itself...

but second to none in pacemaker reliability.

For more than 15 years, Telectronics has been a world leader in the research, development and manufacture of cardiac pacemakers.

In fact, the many fundamental technological advances pioneered by Telectronics have made our pacemakers second only to the heart itself in reliability.



For example, Telectronics pioneered:

reliable monolithic integrated microcircuitry – all active components and 90% of the electronic function are carried by only two tiny IC "chips" which have redundant electrical connections bonded ultrasonically to increase reliability in use.

reliable hermetically sealed titanium casing – assures adequate protection of the power source and electronic components in the hostile environment of the body.

reliable 0.5 msec pulse width – for an optimal balance of efficiency and dependability.

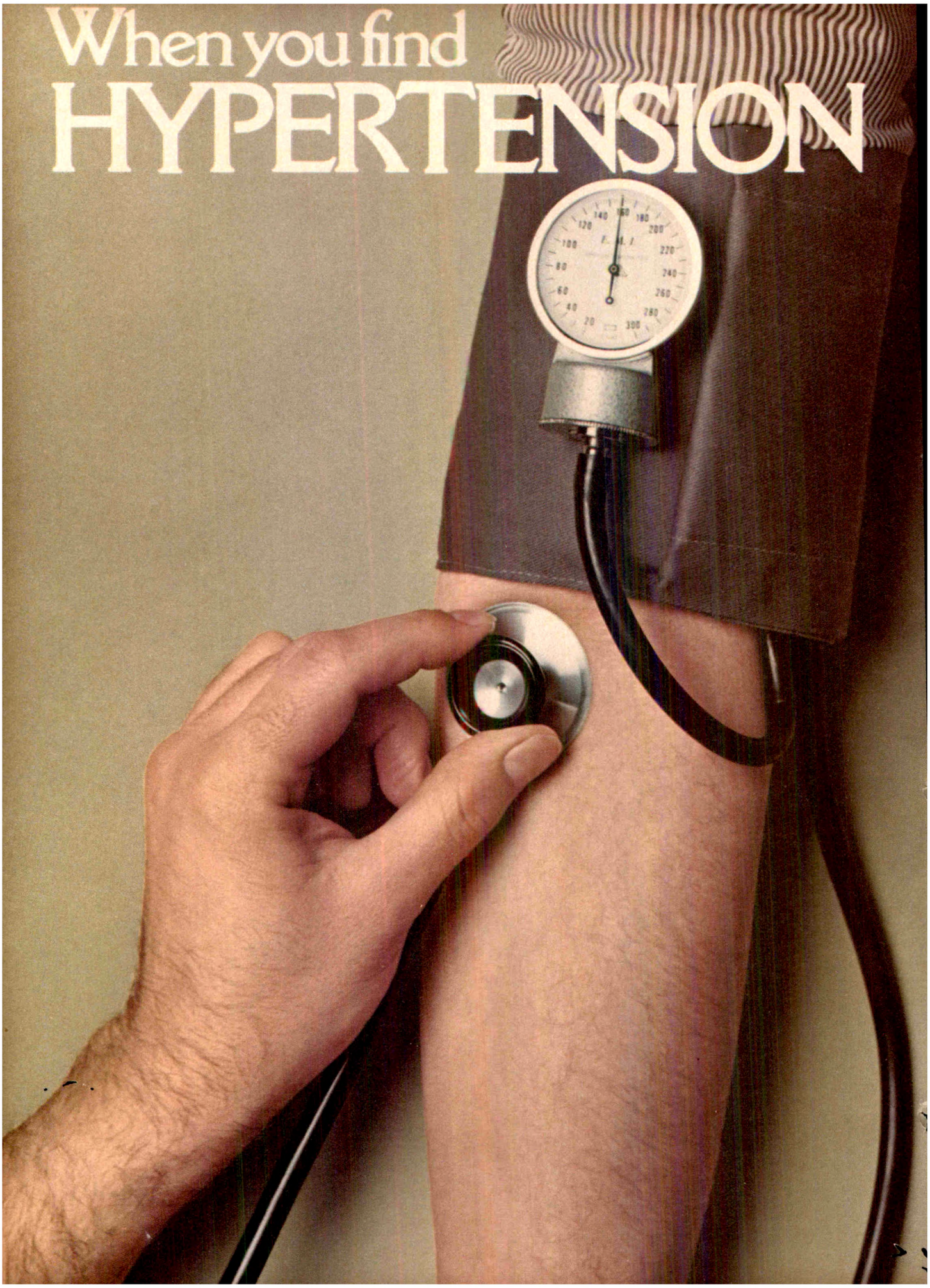
Telectronics also offers:

- ☐ transtelephonic and monitoring equipment for pacemaker follow-up
- ☐ a 24-hour **worldwide** technical service
- ☐ educational material for you and your staff
- ☐ explanatory material for your patients

For additional information about our complete line of pacemakers, electrodes and ancillary products, contact your local Telectronics Representative or Telectronics.

TELECTRONICS

U.S.A. 8560 Main Street, Williamsville, N.Y. 14221, (800) 828-7747 **CANADA** 6299 Airport Road, Mississauga, Ontario L4V1N3, (416) 676-9805
EUROPE The Studio, 61 Carlton Hill, London NW8 OEN, UK (Telex: (51) 27950)
AUSTRALIA (and the rest of the world) 2 Sirius Road, Lane Cove, Sidney, N.S.W. 2066 (Telex: Medtel AA20576)


When you find
HYPERTENSION



Two out of every five hypertensives found to be hyperlipidemic in recent study[1]

Lipid abnormalities are often part of a broader clinical picture. For example, a recent study[1] reports an association between hypertension and hypertriglyceridemia—the most common form of hyperlipidemia. (See table below.)

Type of Hyperlipidemia*	Incidence of Hyperlipidemia	
	Hypertensives (89 subjects)	Normotensives (89 subjects)
Type IIA	9% (8)	7% (6)
Type IIB	6% (5)	3% (3)
Type IV	26% (23)	11% (10)
Total	**41% (36)**	**21% (19)**

*Hyperlipidemia was diagnosed when cholesterol levels exceeded 282 mg% and/or triglycerides were over 177 mg%—cutoff points higher than the usual upper limits of normal. Adapted from Thomas, G. W., *et al.*[1]

The essential measurements–cholesterol *and* triglycerides

Today, lipid determinations are recommended as part of every general medical examination.

Because elevated lipids may coexist with high blood pressure, it is especially important to screen hypertensive patients for hyperlipidemia. Testing for both cholesterol *and* triglycerides is considered essential,[2-5] since it increases the chances of detection from 6 out of 10 to 9.5 out of 10.[6]

See next page of this advertisement for prescribing information.

Hyperlipidemia/**Atromid-S**® (clofibrate) Ayerst

When you find HYPERTENSION Look for HYPERLIPIDEMIA

Atromid-S® (clofibrate)

(For full prescribing information, see package circular.)

ATROMID-S® Brand of clofibrate

Antilipidemic agent for reduction of elevated serum lipids

INDICATIONS: ATROMID-S is indicated as adjunctive therapy in patients who do not respond adequately to diet and other measures for the reduction of elevated serum cholesterol (especially the beta lipoprotein fraction) and/or triglycerides. Clofibrate appears to have a greater depressant effect on the very low density lipoproteins (S_f 20-400) rich in triglycerides than the low density lipoproteins (S_f 0-20) rich in cholesterol.

ATROMID-S is also indicated for treatment of patients with xanthoma tuberosum associated with hyperlipidemia. The skin lesions frequently regress with clofibrate.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CONTRAINDICATIONS: Clofibrate is contraindicated in pregnant women. While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than that found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

It is contraindicated in lactating women since it is not known if clofibrate is secreted in the milk.

It is contraindicated in patients with clinically significant hepatic or renal dysfunction.

It is contraindicated in patients with primary biliary cirrhosis since it may raise the already elevated cholesterol in these cases.

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Strict birth control procedures must be exercised by women of childbearing potential. In patients who plan to become pregnant, clofibrate should be withdrawn several months before conception. Because of the possibility of pregnancy occurring despite birth control precautions in patients taking clofibrate, the possible benefits of the drug to the patient must be weighed against possible hazards to the fetus.

Administration of clofibrate to mice and rats in long-term studies at eight times the human dose resulted in a higher incidence of liver tumors than in controls. Lower doses were not studied. Although the relevance of this finding to humans is not known at this time, it cannot be dismissed especially since this drug is intended for long-term administration. ATROMID-S should be used only in patients with hyperlipidemia who do not respond adequately to dietary intervention.

PRECAUTIONS: Before instituting therapy with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.

Because of the long-term administration of a drug of this nature, adequate baseline studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be obtained during the first few months of ATROMID-S administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, the drug should be employed for longer periods (even up to one year) provided that there is a reduction in the size and/or number of the xanthomata.

Subsequent serum lipid determinations should be done to detect a paradoxical rise in serum cholesterol or triglyceride levels. Clofibrate will not alter the seasonal variations of serum cholesterol peak elevations in midwinter and late summer and decreases in fall and spring. If the drug is discontinued, the patient should be placed on an appropriate hypolipidemic diet, and his serum lipids should be monitored until stabilized, as a rise in these values to or above the original baseline may occur.

During clofibrate therapy, frequent serum transaminase determinations and other liver function tests should be performed since the drug may produce abnormalities in these parameters. These effects are usually reversible when the drug is discontinued. Hepatic biopsies are usually within normal limits. If the hepatic function tests steadily rise or show excessive abnormalities, the drug should be withdrawn. Therefore use with caution in those patients with a past history of jaundice or hepatic disease.

Clofibrate may produce "flu like" symptoms (muscular aching, soreness, cramping). The physician should differentiate this from actual viral and/or bacterial disease.

Use with caution in patients with peptic ulcer since reactivation has been reported. Whether this is drug-related is unknown.

Complete blood counts should be done periodically since anemia, and more frequently, leukopenia, have been reported in patients who have been taking clofibrate.

Various cardiac arrhythmias have been reported with the use of clofibrate.

Several investigators have observed in their studies that clofibrate may produce a decrease in cholesterol linoleate but an increase in palmitoleate and oleate, the latter being considered atherogenic in experimental animals. The significance of this finding is unknown at this time.

ADVERSE REACTIONS: Of the pertinent reactions, the most common is nausea. Less frequently encountered gastrointestinal reactions are vomiting, loose stools, dyspepsia, flatulence, and abdominal distress. Reactions reported less often than gastrointestinal ones are headache, dizziness, and fatigue; muscle cramping, aching, and weakness; skin rash, urticaria, and pruritus; dry brittle hair, and alopecia.

The following reported adverse reactions are listed alphabetically by systems:

Cardiovascular
- Increased or decreased angina
- Cardiac arrhythmias
- Both swelling and phlebitis at site of xanthomas

Dermatologic
- Skin rash
- Alopecia
- Allergic reaction including urticaria
- Dry skin and dry brittle hair
- Pruritus

Gastrointestinal
- Nausea
- Diarrhea
- Gastrointestinal upset (bloating, flatulence, abdominal distress)
- Hepatomegaly (not associated with hepatotoxicity)
- Gallstones
- Vomiting
- Stomatitis and gastritis

Genitourinary
- Impotence and decreased libido
- Findings consistent with renal dysfunction as evidenced by dysuria, hematuria, proteinuria, decreased urine output. One patient's renal biopsy suggested "allergic reaction."

Hematologic
- Leukopenia
- Potentiation of anticoagulant effect
- Anemia
- Eosinophilia

Musculoskeletal
- Myalgia (muscle cramping, aching, weakness)
- "Flu like" symptoms
- Arthralgia

Neurologic
- Fatigue, weakness, drowsiness
- Dizziness
- Headache

Miscellaneous
- Weight gain
- Polyphagia

Laboratory Findings
- Abnormal liver function tests as evidenced by increased transaminase (SGOT and SGPT), BSP retention, and increased thymol turbidity
- Proteinuria
- Increased creatine phosphokinase

Reported adverse reactions whose direct relationship with the drug has not been established: peptic ulcer, gastrointestinal hemorrhage, rheumatoid arthritis, tremors, increased perspiration, systemic lupus erythematosus, blurred vision, gynecomastia, thrombocytopenic purpura.

DOSAGE AND ADMINISTRATION: *Initial:* The recommended dosage for adults is 2 g daily, in divided doses. Some patients may respond to a lower dosage.

Maintenance: Same as for initial dosage.

Note: In children, insufficient studies have been done to show safety and efficacy.

DRUG INTERACTIONS: Caution should be exercised when anticoagulants are given in conjunction with ATROMID-S. The dosage of the anticoagulant should be reduced usually by one-half (depending on the individual case) to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has been stabilized.

MANAGEMENT OF OVERDOSAGE: While there has been no reported case of overdosage, should it occur, symptomatic supportive measures should be taken.

HOW SUPPLIED: ATROMID-S—No. 243—Each capsule contains 500 mg clofibrate, in bottles of 100.

References: 1. Thomas, G. W., *et al.*: Br. Med. J. 2:805 (Sept. 24) 1977. **2.** Ahrens, E. H., Jr.: Ann. Intern. Med. 85:87 (July) 1976. **3.** Council on Foods and Nutrition: J.A.M.A. 222:1647 (Dec. 25) 1972. **4.** Scheig, R.: Conn. Med. 39:71 (Feb.) 1975. **5.** Letters to the Editor: Current Prescribing (July) 1977, p. 15. **6.** Fredrickson, D. S., *et al.*, in Holmes, W. L., Carlson, L. A., and Paoletti, R.: Drugs Affecting Lipid Metabolism, Vol. 4, New York, Plenum Press, 1969, p. 314. **7.** Brown, H. B., Lewis, L. A., and Page, I. H.: Clin. Pharmacol. Ther. 17:171 (Feb.) 1975. **8.** Gelfand, M. L., and Garbor, M.: Exhibit, American College of Cardiology Meeting, New Orleans, La., Feb. 21-Mar. 1, 1970. **9.** Zelis, R., *et al.*: J. Clin. Invest. 49:1007 (May) 1970. **10.** Levy, R. I., *et al.*: Ann. Intern. Med. 77:267 (Aug.) 1972. **11.** Berkowitz, D.: J.A.M.A. 218:1002 (Nov. 15) 1971. **12.** Lorenzo, E. M., *et al.*: Curr. Ther. Res. 22:147 (July, Sect. 2) 1977.

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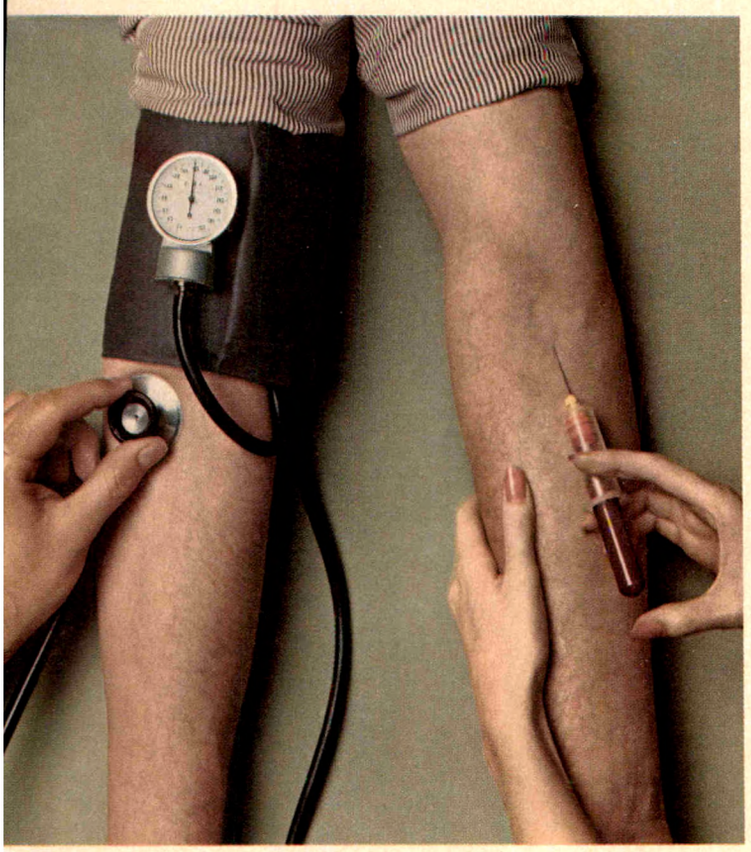
7808

When diet alone is not enough

Atromid-S®

(clofibrate) Capsules 500 mg

The most widely prescribed antilipemic agent–significantly lowers serum levels of cholesterol and/or triglycerides



Proved effective in study after study

In clinical studies involving patients with drug-responsive hyperlipoproteinemia, diet plus ATROMID-S (clofibrate) lowered serum cholesterol levels from 22% to as much as 52% and reduced triglyceride values over a range of 19% to 80%.[7-12]

Patient acceptance is generally good

In more than a decade of use, clofibrate has been generally well tolerated. Major adverse effects are primarily gastrointestinal, with nausea being predominant. Other G.I. reactions include loose stools, flatulence, abdominal distress, and, infrequently, gallstones. Less common reactions include muscle cramping, myalgia, and alopecia. Please see "Important Note" below and Warning on concomitant anticoagulant usage in prescribing information on adjacent page.

AN IMPORTANT NOTE: It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

See adjacent page of this advertisement for prescribing information.

A reminder
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(digoxin)



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yellow
imprinted

0.25 mg
white
imprinted & scored

0.5 mg
green
imprinted & scored

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VOLUME 41

NUMBER 5

CLINICAL STUDIES

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Sudden death is a recognized complication in symptomatic patients with hypertrophic cardiomyopathy. However, its occurrence in patients with no or transient previous cardiac symptoms presents a particularly challenging diagnostic and therapeutic dilemma. Therefore, 26 patients with hypertrophic cardiomyopathy whose death was the first definitive manifestation of cardiac disease were evaluated. Their ages ranged from 8 to 49 years (mean 18) and 23 were less than 25 years of age; 19 were male and 7 female. Of the 26 patients, 13 died during or immediately after moderate or severe physical exertion. Of 12 patients with previous cardiac catheterization, 6 had no or a small left ventricular outflow tract gradient under basal conditions and 6 had an outflow gradient of 50 mm Hg or greater. Left ventricular end-diastolic pressure was elevated in nine patients, and the ventricular septum was moderately to severely thickened (17 mm or more) in all patients. The electrocardiogram was abnormal in all 19 patients studied before death. Thus, sudden death may be the first definitive manifestation of cardiac disease in some patients with hypertrophic cardiomyopathy. Although the effects of patient selection in this study group cannot be excluded, sudden death was common in children and young adults and was often related to physical exertion; each patient showed a distinctly abnormal electrocardiogram and moderate to severe ventricular septal thickening.

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Hypertrophic cardiomyopathy is a genetically transmitted disease of cardiac muscle characterized by disproportionate thickening of the ventricular septum.[1–7] Sudden and unexpected death is a recognized complication in symptomatic adults and children with this disease.[8–13] Patients with hypertrophic cardiomyopathy who were asymptomatic or experienced only rare transient symptoms before death have been described occasionally[8,10–15] but not in detail or in a manner permitting proper characterization of this subgroup. Nevertheless, identification and subsequent management of such patients with hypertrophic cardiomyopathy presents particularly difficult problems. Therefore, to define and characterize more clearly this subgroup, we analyzed the clinical and morphologic features of 26 patients with hypertrophic cardiomyopathy whose first definitive symptomatic manifestation of cardiac disease was death.

TABLE I

Clinical, Hemodynamic and Pathologic Data in 26 Cases

Case no.	Age (yr) & Sex	Electrocardiogram	Hemodynamics: LVOT Gradient Basal	Hemodynamics: LVOT Gradient Provocation	Hemodynamics: LV Pressure	Hemodynamics: RVOT Gradient	Hemodynamics: CI	Circumstances of Death	Family History SD	Necropsy: Heart Weight (g)	Necropsy: VS	Necropsy: PW	Necropsy: VS/PW	Necropsy: Disorganized Cells in VS	Possible Cardiac Symptoms
1	8M	–	–	–	–	–	–	After hiking	0	350	25	13	1.9	+	0
2	10M	LVH	–	–	–	–	–	Stepped out of school bus*	+	–	Marked VS hypertrophy[d]			+	0
3	11F	–	–	–	–	–	–	After mild calisthenics	0	400	17	9	1.9	+	1 episode syncope 3 wk before death
4	11M	LAD; probable LVH; LAE; ST-T changes	5	35	92/29	0	3.9	After light play	0	–	–	–	–	–	0
5	12M	ST-T changes[‡]	–	–	–	6	–	Jogging**	+	270	18	10	1.8	+	0
6	13M	–	–	–	–	–	–	After recreational ball game	+	375	25	17	1.5	–	0
7	14M	LVH with "strain"[§]; diffuse T wave inversion; Q wave in leads II, III, aVF, V_6	13	–	110/24	0	3.0	After walking up steep hill	+	360	20	10	2.0	+	0
8	15F	LVH; Q waves in leads I, aVL, V_5V_6; S-T depressed in I, aVL	–	–	–	–	–	Sedentary activity	0	320	22	11	2.0	+	Lightheadedness
9	15F	LVH; marked LAD; Q waves in leads I, II, III, aVF, V_5, V_6; S-T elevated in II, III, aVF, V_6	50	95	157/20	–	6.0	Stepping out of car	0	550	34	20	1.7	–	0
10	15F	LVH with "strain"; Q waves in lead aVL; LAD; LAE; ST-T changes[a]	10-55	115	110-155/30	15	3.7	Running	+	400	38	16	2.4	+	1 episode dyspnea, lightheadedness during running 5 mo before death
11	15F	LVH[ϕ]; ST-T changes; poor progression of precordial R waves; LAE	100	–	200/24	–	3.0	Running	+	550 (est)	36	14	2.6	+	0
12	15M	–	–	–	–	–	–	During recreational basketball	+	475	–	–	–[e]	–	0

Table I (continued)

Case no.	Age (yr) & Sex	Electrocardiogram	Hemodynamics: LVOT Gradient Basal	Hemodynamics: LVOT Gradient Provocation	Hemodynamics: LV Pressure	Hemodynamics: RVOT Gradient	Hemodynamics: CI	Circumstances of Death	Family History SD	Necropsy: Heart Weight (g)	Necropsy: VS	Necropsy: PW	Necropsy: VS/PW	Necropsy: Disorganized Cells in VS	Possible Cardiac Symptoms
13	16M	LVH; LAE; Q wave in lead V_6; T wave inversion in leads II, III, aVF; P-R = 0.10	75	–	175/20	0	4.4	After light play	0	520	–	–	–	–	1 episode syncope 1 yr before death
14	16F	Deep Q wave in leads III, aVF; possible RVH	–	–	–	–	–	Jogging	+	310	21	8	2.6	+	0
15	17M	LVH[g]; LAD; T wave inversion in leads I, aVL; S-T elevated in V_1V_2	60	–	140/16	0	4.7	Sedentary	0	–	27[f]	17	1.6	–	0
16	17M	–	–	–	–	–	–	Jogging	0	530	21	12	1.8	+	0
17	17M	–	–	–	–	–	–	During competitive basketball game	0	740	–	–	–[b]	+	Lightheadedness
18	19M	LVH with "strain"[δ]; Q wave in lead V_6; S-T elevated in V_1-V_3	15	50	136/12	8	4.2	Running	0	900	55	30	1.8	–	Lightheadedness
19	21F	T wave inversion in leads III, aVF; LAE; possible LVH	–	–	–	–	–	Walking[θ]	0	400	24	9	2.7	+	1 episode syncope 3 yr before death; lightheadedness: paroxysmal AF and other SVT + PVCs
20[c]	21M	LVH; LAD; poor progression of precordial R waves; QS waves in leads III, aVF, V_1; S-T elevated in V_1-V_3; LAE	65	–	185/16	10	3.3	Mild exertion; throwing football	0	–	–	–	–	–	0
21	22M	LAD; possible LVH; Q waves in leads II, III, aVF[†]	–	–	–	–	–	Running up a grade	+	610	35	21	1.7	+	0

Table I (continued)

Case no.	Age (yr) & Sex	Electrocardiogram	Hemodynamics: LVOT Gradient Basal	Hemodynamics: LVOT Gradient Provocation	Hemodynamics: LV Pressure	Hemodynamics: RVOT Gradient	Hemodynamics: CI	Circumstances of Death	Family History SD	Necropsy: Heart Weight (g)	Necropsy: VS	Necropsy: PW	Necropsy: VS/PW	Necropsy: Disorganized Cells in VS	Possible Cardiac Symptoms
22	23M	LVH; deep T wave inversion; VT with exertion	0	–	130/5	0	3.3	During recreational basketball game	0	500	20	15	1.3	0	0
23	23M	–	–	–	–	–	–	Sedentary activity	0	750	30	15	2.0	+	0
24	29M	Probable LVH; LAD;IVCD; 1^0 AVB (P-R =) 0.24)	0	0	110/12	0	3.7	Dived in ocean surf$^{\Delta}$	0	450	25	12	2.1	+	Lightheadedness; occasional palpitations
25	31M	RBBB; Q waves in lead aVL	–	–	–	–	–	During mild calisthenics	0	450	24	12	2.0	+	0
26	49M	LVH with "strain"; LAD; ST-T changes; Q waves in leads I, aVL	20	30	130/15	15	3.3	Watching television	0	–	–	–	–	–	A Fl (2:1 block) with diaphoresis and pallor 3 mo before death

Case numbers in boldface italics indicate siblings from two families; that is, Patients 2, 6 and 12 and Cases 5 and 7 are siblings.

AF = atrial fibrillation; A Fl = atrial flutter; CI = cardiac index (liters/min per m^2); est = estimated; 1^0AVB = first degree atrioventricular block; IVCD = intraventricular conduction defect; LAD = left axis deviation; LAE = left atrial enlargement; LV Pressure = left ventricular pressure (systolic/diastolic) (mm Hg); LVH = left ventricular hypertrophy; LVOT gradient = left ventricular outflow tract pressure gradient (mm Hg); MV = mitral valve; PVC = premature ventricular complexes; PW = posterior left ventricular free wall (mm); RAD = right axis deviation; RBBB = right bundle branch block; RVH = right ventricular hypertrophy; RVOT gradient = right ventricular outflow tract pressure gradient (mm Hg); SD = sudden death; SVT = supraventricular tachycardia; VS = ventricular septum (mm); VS/PW = ventricular septal to posterobasal left ventricular free wall ratio; VT = ventricular tachycardia.

* Previous cardiac arrest after mild exertion, 20 months before death; this patient died 8 days after his brother (Case 6).

† Electrocardiograms obtained at age 14 to 20 years showed right axis deviation and right ventricular hypertrophy.

‡ Electrocardiogram obtained 5 weeks after cardiac arrest; no tracing recorded before arrest.

** Ventricular fibrillation documented after collapse; patient survived in coma for 5 weeks with evidence of cerebral anoxia; transmural ventricular septal infarct present at necropsy.

Δ Previous cardiac arrest while running, 8 months before death; ventricular fibrillation documented after collapse; atrial flutter after syncopal spell, 1 month before death.

§ Appearance of "strain pattern" (left ventricular hypertrophy with secondary ST-T abnormalities) 7 months before death.

δ Appearance of "strain pattern" (left ventricular hypertrophy with secondary ST-T abnormalities) 3 1/2 years before death.

ϕ RAD present at age 12 years; normal QRS axis present at age 13 and subsequently.

θ Ventricular fibrillation documented after collapse; patient survived 2 hours.

[a] Electrocardiogram normal at age 10 years, abnormal at age 12 and subsequently.

[b] Although ventricular wall thickness data were not available in this patient, the presence of echocardiographically determined asymmetric septal hypertrophy in his mother and brother and the presence of disorganized cardiac muscle cells in his ventricular septum provide strong presumptive evidence that he had hypertrophic cardiomyopathy.

[c] Patient had documented cardiac arrest (ventricular fibrillation), was successfully resuscitated and has survived with evidence of severe cerebral anoxia.

[d] Exact wall thickness measurements not available.

[e] Wall thickness measurements not available; diagnosis of hypertrophic cardiomyopathy is a presumptive one, based on the presence of cardiac hypertrophy and a strong family history of hypertrophic cardiomyopathy.

[f] Measurements of ventricular septal and posterobasal left ventricular wall thicknesses made with echocardiography[15] 5 months before death; measurements of ventricular septal thickness with echocardiography and subsequently at necropsy usually agree closely.[20]

[g] RAD, RVH present at age 5 years; normal QRS axis, poor R wave progression and deep Q wave in lead aVL at age 9 years; normal electrocardiogram except for Q wave in lead aVL at age 10 years; left ventricular hypertrophy at age 14 and subsequently.

– Data not available.

+ Present.

0 Absent.

Methods

Selection of patients: The study group was divided into two subgroups: Group I, 17 patients with hypertrophic cardiomyopathy who had no cardiac symptoms before death, and Group II, 9 patients who were asymptomatic except for rare transient symptoms that may have been due to hypertrophic cardiomyopathy. Group II included three patients with a single syncopal episode, one patient with an episode of mild dyspnea and lightheadedness while running, one patient with one episode of atrial flutter (2:1 block; ventricular rate 150/min) and four patients with lightheadedness. None of these nine patients were evaluated initially because of their symptoms.

Two patients in Group I had ventricular fibrillation and cardiac arrest from which they were successfully resuscitated before death; another patient in Group I experienced ventricular fibrillation. For convenience, we have equated ventricular fibrillation with actual cardiac death in these three patients.

Patients were selected from the case records of the following sources: National Heart, Lung, and Blood Institute (16 patients), Armed Forces Institute of Pathology Cardiovascular Registry (2 patients), United Hospitals-Miller Division Cardiovascular Registry (4 patients) and Children's Hospital of Pittsburgh (4 patients). The diagnosis of hypertrophic cardiomyopathy was confirmed in 23 patients at necropsy or with echocardiography (ventricular septal to left ventricular free wall thickness ratio of 1.3 or more) or on the basis of the typical clinical and hemodynamic features of hypertrophic cardiomyopathy. In the remaining three patients the diagnosis of hypertrophic cardiomyopathy was made presumptively, on the basis of presence of cardiac hypertrophy and a confirmed family history of hypertrophic cardiomyopathy.

Description of patients: The patients ranged in age from 8 to 49 years (mean 18); 23 of the 26 patients were less than 25 years old at death. Nineteen patients were male and 7 female; 24 were white and 2 black. Nineteen of the 26 patients had a cardiac evaluation before death. Right and left heart hemodynamic studies were performed in 12 of these patients from 6 months to 11 years (median 2 1/2 years) before death, usually because of the presence of a heart murmur, abnormal electrocardiogram or family history of heart disease or sudden death. Five patients were competitive athletes, including one who had competed on his varsity college basketball team for 4 years without evidence of limitation. There were two sets of siblings, two patients from one family and three from another. Four other patients had at least one first degree relative who died suddenly of hypertrophic cardiomyopathy.

Results

No differences in any of the following variables were found between the two patient groups. The clinical, hemodynamic and pathologic findings in each of the study patients are summarized in Table I.

Physical findings: Four patients had not had an adequate cardiac physical examination before death. Heart murmurs were present in 16 of the remaining 22 patients. These murmurs, first identified from birth to age 28 years, were usually grade 2 to 3/6 systolic ejection murmurs heard loudest at the lower left sternal border or apex. In the other six patients no murmur had been identified.

Chest radiographic findings: Heart size was normal in 14 of the 17 patients who had a chest radiograph taken; the remaining three patients had a cardiothoracic ratio of 0.55 to 0.60. No patient had abnormal pulmonary arterial or venous markings on X-ray examination.

TABLE II

Electrocardiographic Abnormalities in 19 Patients

	Patients (no.)	
Left ventricular hypertrophy	15	
Probable		10
Possible		2
With "strain" pattern*		4
S-T segment and T wave abnormalities	14	
Abnormal Q or QS†	10	
Left axis deviation	8	
Left atrial enlargement	5	
Right bundle branch block	1	
First degree atrioventricular block	1	
Intraventricular conduction defect	1	
Marked diffuse T wave inversion (ventricular tachycardia with exercise)	1	
Possible right ventricular hypertrophy	1	

* Tall voltages in the left precordial leads associated with secondary S-T segment and T wave changes.
† 4 or more mm in depth or 0.04 second in duration, in one or more leads.

Electrocardiographic findings: Electrocardiograms were obtained in 19 of the 26 patients and were abnormal in each (Table II). Although no electrocardiographic pattern was entirely characteristic of the study group, the most common abnormalities were left ventricular hypertrophy, S-T segment and T wave changes and deep, wide Q waves.

In six patients the electrocardiographic pattern changed 7 months to 4 years before death. A left ventricular "strain" pattern developed in three of these patients, including one with a previously normal electrocardiogram. In three other patients the electrocardiograms initially revealed right ventricular hypertrophy or right axis deviation, or both, but later were consistent with left ventricular hypertrophy.

Only one patient demonstrated premature complexes in the routine electrocardiogram; however, one other patient (Case 22) did show ventricular tachycardia (6 seconds' duration) and frequent premature ventricular complexes during the course of a routine treadmill stress test. In five patients ventricular fibrillation was documented after the patient's sudden collapse. One of these patients (Case 24) also had atrial flutter with variable block (3:1 to 6:1) after a severe syncopal episode 7 months after his initial cardiac arrest and 1 month before death. Another patient (Case 26) also demonstrated atrial flutter (with 2:1 block), associated with diaphoresis and pallor, 3 months before death.

Hemodynamic and angiographic data: *Right and left heart hemodynamic studies* were performed in 12 cases. In 6 of the 12 patients peak systolic left ventricular outflow tract pressure gradients of 50 mm Hg or greater were present under basal conditions (Fig. 1). In the remaining six patients, either no outflow gradient (two patients) or a small gradient of 20 mm Hg or less (four patients) was present. One patient with a 5 mm Hg

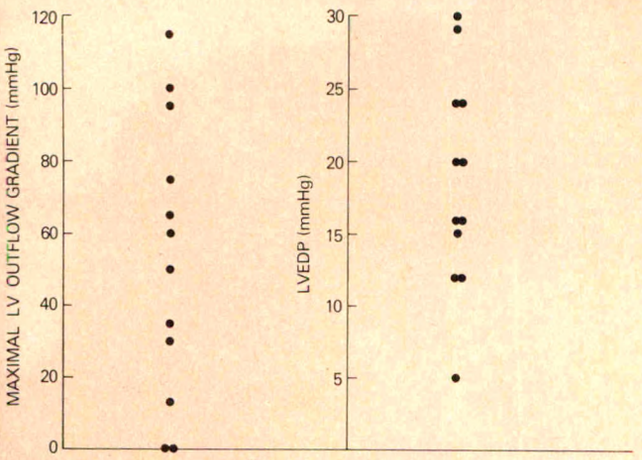


FIGURE 1. Left ventricular (LV) outflow gradients (maximal under basal conditions or with provocation) and left ventricular end-diastolic pressures (LVEDP) in the 12 patients with such measurements.

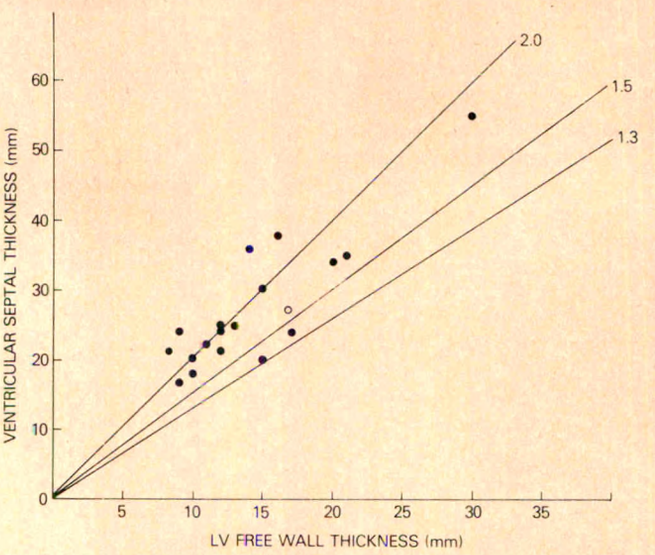


FIGURE 2. Ventricular septal and left ventricular (LV) free wall thicknesses in the 19 patients in whom such measurements were obtained. **Identity lines** define septal/free wall ratios of 1.3, 1.5 and 2.0. **Open symbol** denotes a patient whose ventricular septal and left ventricular free wall thicknesses were measured with echocardiography during diastole 5 months before death.

gradient under basal conditions had a 35 mm Hg gradient with provocation with isoproterenol infusion, and another with a 15 mm Hg gradient under basal conditions had a 50 mm Hg gradient with provocation. Five of the 12 patients had a relatively small peak systolic gradient of 6 to 15 mm Hg between the right ventricle and pulmonary artery. Left ventricular end-diastolic pressure ranged from 5 to 30 mm Hg and was elevated (more than 12 mm Hg) in 9 of the 12 patients (Fig. 1).

Left ventricular angiography was performed in nine patients. In five of these patients, the study showed obliteration of the left ventricular apex during systole, a finding considered characteristic of hypertrophic cardiomyopathy. Two other patients showed severe narrowing of the mid left ventricular cavity during systole that appeared to be due to papillary muscle encroachment. In the remaining two patients, left ventricular contraction was considered normal although deformities in the contour of the left ventricle suggested bulging of a hypertrophied ventricular septum into the left ventricular cavity.

Circumstances of death: Cardiac arrest was sudden and occurred without warning in each of the 26 patients. In 23 patients death occurred instantaneously or within a few minutes. Of the other three patients, one (Case 5) was resuscitated and survived 5 weeks after cardiac arrest with evidence of severe cerebral anoxia, and another (Case 19) survived 2 hours after cardiac arrest; the remaining patient (Case 20) had an episode of ventricular fibrillation, was successfully resuscitated and has survived to date. In 2 of the 26 patients the fatal cardiac arrest was preceded by an initial cardiac arrest that occurred 20 (Case 2) and 8 (Case 24) months earlier. None of the 26 patients were hospitalized at the time of the initial cardiac arrest.

Death occurred during sedentary or normal activities in 6 patients, during or just after mild exertion in 7 and during or just after moderate or severe exertion in 13. No patient died during sleep.

Necropsy findings: Heart weight ranged from 270 to 900 g (median 450) and was increased with respect to age in each patient.[16] In 18 patients either the heart was in suitable condition for detailed examination or sufficient pathologic information was available to assign a septal/free wall ratio. In one other patient (Case 15), in whom necropsy was not performed, measurements of ventricular septal and posterobasal left ventricular wall thicknesses were obtained with echocardiography[2] 5 months before death. Each of these 19 hearts showed disproportionate thickening of the ventricular septum with respect to the left ventricular free wall (septal/free wall ratio 1.3 or more[2,17]) (Fig. 2). Septal/free wall ratios ranged from 1.3 to 2.7 (median 1.9). Absolute ventricular septal thickness ranged from 17 to 55 mm (median 25); in all but two patients septal thickness was 20 mm or greater. The two patients in this study with a septal thickness of less than 20 mm (17 and 18 mm) were only 11 and 12 years of age, respectively (Cases 3 and 5). One patient (Case 5), who survived for 5 weeks after cardiac arrest, had a large transmural ventricular septal infarct despite widely patent extramural coronary arteries; none of the other hearts had areas of transmural scarring or evidence of coronary artery disease (more than 50 percent cross-sectional narrowing of a coronary arterial lumen).

Of the 17 hearts in which the mitral valve and endocardial surface of the left ventricular outflow tract could be studied, 8 showed an endocardial contact plaque on the ventricular septum adjacent to a thickened anterior mitral leaflet. One patient had only an endocardial plaque, one only a thickened anterior mitral leaflet and seven patients had neither an endocardial plaque nor a thickened mitral leaflet.

In 16 of the 17 patients with histologic studies, numerous cardiac muscle cells in the ventricular septum showed a disorganized arrangement characteristic of hypertrophic cardiomyopathy.[15,18,19] In another patient disorganization was only minimal. Microscopy in the remaining patient, who demonstrated the typical gross anatomic features of hypertrophic cardiomyopathy, revolved normally arranged cardiac muscle cells in the ventricular septum.

Morphologic observations regarding arrangement of cardiac muscle cells in the left ventricular free wall were made in 15 of the 17 patients. Six of the 15 had numerous disorganized cardiac muscle cells in the left ventricular free wall, 2 had mild disorganization and 7 had a normal arrangement of virtually all cardiac muscle cells in the left ventricular free wall.

Therapy: Seven of the 26 patients had been treated with propranolol. Each of these patients was under treatment at the time of death and had been taking propranolol for 3 months to 2 1/2 years. The dose of propranolol was considered adequate (2 or more mg/kg per day) in three patients and inadequate in the other four. Six of these patients were given propranolol in the hope of arresting progression of disease; the seventh was given propranolol because of an episode of atrial flutter.

Discussion

Our results indicate that sudden death is not rare in patients with hypertrophic cardiomyopathy who previously did not manifest functional limitation. Moreover, children and young adults appear to be particularly susceptible to sudden death: 23 of our 26 patients were less than 25 years of age at death.

Characteristic clinical features: Two clinical features were characteristic of this unique population of patients: (1) a distinctly abnormal electrocardiogram, and (2) a moderately to severely thickened ventricular septum. Although this latter finding is based on necropsy measurements, we have previously shown a relatively close correlation between measurements of ventricular septal thickness obtained with echocardiography and subsequently at necropsy in patients with disproportionate septal thickening.[20] Our finding of moderate to severe ventricular septal thickening in the patients in our study group has potentially important clinical implications, but one must be aware of the possible influence of patient selection. For example, it may be less likely that patients with hypertrophic cardiomyopathy and only a mildly hypertrophied septum would be systematically identified as having this disease at necropsy. Therefore, such patients may not have been referred to us. Nevertheless, our findings that a distinctly abnormal electrocardiogram and moderate to severe ventricular septal thickening were characteristic of our study group are highly relevant to any future prospective studies designed to identify the risk factors for sudden death in patients with hypertrophic cardiomyopathy.

No clinical or hemodynamic variable was an entirely reliable predictor of death in our patients. These variables included radiographically determined heart size, specific electrocardiographic abnormality and left ventricular end-diastolic pressure. Although previous investigators[12] have suggested that elevated left ventricular end-diastolic pressure is a poor prognostic sign in patients with hypertrophic cardiomyopathy, this was not true in the present study group or in our previous study[13] of children with hypertrophic cardiomyopathy. Although 6 of the 12 patients had markedly elevated left ventricular end-diastolic pressure (20 mm Hg or greater), 3 had only mildly elevated pressure (15 to 16 mm Hg) and 3 had a normal pressure (12 mm Hg or less). However, 6 of our 25 patients showed electrocardiographic evidence of increasing left ventricular overload within 4 years of the time of death. Hence, such an evolution in the electrocardiographic pattern may be an early sign of impending sudden death in some patients with hypertrophic cardiomyopathy even though there may be no symptomatic evidence of disease.

Therapeutic implications: Treatment with propranolol did not appear to be entirely protective against sudden death in our patients. Seven patients had been taking propranolol before and at the time of death; but the dosage could be considered adequate (2 or more mg/kg per day) in only three. Moreover, we do not know the role that patient selection played in these data, that is, how many patients at risk of sudden death did not die *because* they were taking propranolol. Hence, the available data are inconclusive regarding the potential efficacy of propranolol administered prophylactically in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy.

Mechanisms of sudden death: Although the exact mechanism of sudden death in patients with hypertrophic cardiomyopathy is not known, ventricular arrhythmias have been suggested as the terminal event.[13] Our finding that four patients had ventricular fibrillation immediately after their collapse supports this contention. It also is not uncommon to observe frequent ventricular premature complexes in such patients.[21] However, our data also raise the possibility that atrial arrhythmias play an etiologic role in the precipitation of ventricular fibrillation in some patients with hypertrophic cardiomyopathy. For example, one patient (Case 26) was completely asymptomatic until age 49 years, when he experienced an episode of atrial flutter; he died suddenly 3 months later. Another patient (Case 24), who experienced two cardiac arrests, had atrial flutter documented immediately after a syncopal spell 1 month before his death. Thus, it is possible (but purely speculative) that rapid supraventricular tachycardias lead to inadequate ventricular filling (particularly in hearts with diminished compliance) that then results in hypotension and subsequent cardiac arrest. Alternatively, it is possible that abnormally rapid atrioventricular transmission can occur in patients with hypertrophic cardiomyopathy through accessory conduction pathways and that the extremely rapid ventricular response may ultimately deteriorate into ventricular fibrillation.

Family history: About one third of our 26 patients had a family history of sudden cardiac death in a first degree relative (including siblings in two instances). This finding suggests that sudden death is more prevalent in some families with hypertrophic cardiomyopathy and that a history of sudden death in a closely related relative may be a poor prognostic factor for patients with hypertrophic cardiomyopathy. Although about 75 percent of our study patients were male, this prevalence rate does not differ significantly from that of male subjects in the overall population of patients with hypertrophic cardiomypathy (67 percent).[10]

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Electrophysiologic Findings in Patients With Idiopathic Hypertrophic Subaortic Stenosis

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Thirteen patients with catheterization-proved idiopathic hypertrophic subaortic stenosis underwent intracardiac electrophysiologic study. There was a large incidence of arrhythmias and a strikingly large incidence of conduction system abnormalities among these patients. The P-A and A-H intervals were normal in all patients. Atrial pacing resulted in Mobitz type I block proximal to the His bundle at an abnormal rate (less than 140/min) in 2 of 12 patients (17 percent). H-V intervals were prolonged (greater than 50 msec) in 10 of 12 patients (83 percent) and were greater than 60 msec in 7 patients (58 percent). The atrial effective refractory period was prolonged in 3 of 12 patients and was markedly prolonged in 1 of them. Effective refractory period of the atrioventricular (A-V) node, determined in five patients, was prolonged in three. Dual responses of the A-V node to atrial extrastimuli were found in seven patients. Dual A-V nodal responses were evoked with propranolol in three patients and persisted in the other four patients with dual responses despite propranolol administration.

During the past decade the clinical and hemodynamic features of idiopathic subaortic stenosis (obstructive cardiomyopathy) have been described in detail, and the principles of medical and surgical therapy have been established.[1–8] Several authors have suggested that arrhythmias and electrophysiologic abnormalities in this condition are responsible for the clinical presentation of palpitation, dizziness, syncope and sudden death.[2,3,5–7] Arrhythmias have also been associated with the onset of clinical deterioration.[3,9] We previously reported the large incidence of ventricular and atrial ectopic beats and supraventricular tachycardia in patients with idiopathic hypertrophic subaortic stenosis and the notable lack of efficacy of propranolol as an antiarrhythmic agent in those patients.[10,11]

Despite this large incidence of arrhythmias, little information is available regarding electrophysiologic abnormalities in idiopathic hypertrophic subaortic stenosis. Accordingly, we performed intracardiac electrophysiologic studies and determined the effects of propranolol on the conduction system in 13 patients with previously documented idiopathic hypertrophic subaortic stenosis.

Methods

Patients: Thirteen patients with idiopathic hypertrophic subaortic stenosis confirmed with cardiac catheterization underwent electrophysiologic study. There were 12 men and 1 woman who ranged in age from 35 to 74 years (average 51). Each patient had previously been evaluated with treadmill testing or ambulatory electrocardiographic monitoring, or both.[10,11] These 13 patients were selected for study from a group of 106 patients with idiopathic hypertrophic subaortic stenosis referred to our institution from 1968 to 1976 because of symptoms (including palpitation, a sense of rapid heart action, presyncope and syncope) that might be attributed to cardiac arrhythmias. The results of cardiac

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TABLE I

Hemodynamic Data of 13 Patients

Case no.	Age (yr) & Sex	Systolic Pressure Gradient (mm Hg) At Rest	Systolic Pressure Gradient (mm Hg) Peak	LVEDP	MR	CI
1	47F	66	116	30	0	2.5
2	45M	31	159	14	0	3.2
3	43M	0	61	12	1+	3.1
4*	55M	0	70	16	0	2.7
5	57M	9	160	16	1+	2.1
6	58M	20	60	6	4+	. . .
7†	62M	4	124	14	1+	2.8
8	58M	21	100	6	2+	3.2
9	48M	0	78	9	0	2.7
10	62M	Variable	103	10	0	2.0
11	39M	0	46	11	0	2.4
12	35M	0	79	20	0	4.6
13	58M	72	130	14	0	2.6

* Data are preoperative.
† Data are postoperative.
CI = cardiac index (liters/min per m^2); LVEDP = left ventricular end-diastolic pressure (mm Hg); MR = mitral regurgitation (0 = none; 1+ = mild; 2+ = moderate; 4+ = severe).

catheterization in these patients are summarized in Table I. Two patients (Cases 4 and 7) had had myomectomy and myotomy 52 months and 11 years, respectively, before this study. Nine patients were receiving propranolol in doses ranging from 40 to 160 mg/day. All medications were discontinued at least 48 hours before electrophysiologic study.

Electrophysiologic studies: Studies were performed using standard His bundle recording techniques. Patients were in a nonsedated postabsorptive state. A quadripolar electrode catheter was inserted into the basilic vein with either a cutdown or a percutaneous technique and positioned high in the right atrium, with the proximal pair of electrodes at the junction of the right atrium and the superior vena cava. The atrial electrogram was recorded from the two distal poles; the two proximal poles were used to pace the atrium. A tripolar electrode catheter with an interelectrode distance of 1 cm was then introduced with the percutaneous technique into the femoral vein and positioned to record a His bundle electrogram. Atrial and His bundle electrograms were filtered below 40 and above 500 hertz and were recorded simultaneously with surface electrocardiographic leads I, aVF and V_1 on an Electronics for Medicine DR-16 or a Hewlett-Packard multichannel physiologic recorder at paper speeds of 100 and 200 mm/sec. Baseline measurements of cycle length (heart rate) and conduction intervals were made for each patient. The P-A interval was measured from the onset of the P wave in the surface electrocardiogram to the onset of atrial depolarization recorded from the tripolar catheter. The A-H interval was measured from the first high frequency deflection of atrial depolarization recorded from the quadripolar catheter to the first high frequency deflection of the bundle of His electrogram. The H-V interval was measured from the first high frequency deflection of the bundle of His electrogram to the earliest onset of ventricular depolarization recorded in one of the three surface electrocardiographic leads. In our laboratory the following values are considered normal: P-A interval, 25 to 45 msec; A-H interval, 60 to 130 msec; and H-V interval, 35 to 50 msec.

Atrial stimuli at twice the diastolic threshold and of 2 msec duration were delivered, using a programmable stimulator (manufactured by M. Bloom, Philadelphia) and a Tektronix square-wave pulse generator, at a rate slightly faster than the patient's resting heart rate. The pacing rate was gradually increased in increments of 10 beats/min until a rate of 150 beats/min was reached. Premature atrial stimuli were then introduced after every eighth beat during spontaneous sinus rhythm and during atrial pacing at a cycle length 25 to 50 msec shorter than the spontaneous cycle length in 12 of the 13 patients. Atrial stimuli were initially introduced late in diastole and then administered progressively earlier in 5 to 10 msec decrements until atrial refractoriness was encountered. Paired stimuli and ventricular extrastimuli were not used.

Definitions: S_1, A_1 and H_1, and S_2, A_2 and H_2 were defined as stimulus artifact, atrial electrogram and His bundle electrogram recorded from the tripolar catheter during spontaneous or basic paced rhythm (subscript 1) and after premature atrial stimulation (subscript 2). The longest A_1-S_2 interval at which atrial capture consistently failed was defined as the atrial effective refractory period. The effective refractory period of the atrioventricular (A-V) node was defined as the longest A_1-A_2 interval at which conduction failed to traverse the A-V node to produce a His potential. The atrioventricular (A-V) nodal functional refractory period was recorded as the shortest H_1-H_2 interval that could be achieved during premature atrial pacing. When dual A-V nodal refractory periods were present, the shorter period was ascribed to a "slow" pathway and the longer period to a "fast" pathway. The relative refractory period of the His-Purkinje system was defined as the longest H_1-H_2 interval at which the V_1-V_2 interval began to exceed H_1-H_2. Normal values for refractory periods have been reported previously.[12]

Propranolol: Eleven patients were given propranolol, 0.15 mg/kg body weight, intravenously over 10 minutes, and 10 minutes after the infusion was completed the studies were repeated. In all patients the serum propranolol concentration was determined at the beginning of the study and at the conclusion of the repeat electrophysiologic studies. Propranolol assays were performed by Ayerst Laboratories, Toronto. The initial serum concentration of propranolol was zero in all patients. On repeat determination the mean concentration for the group was 18.9 ± 2.11 μg/ml (mean ± standard error of the mean).

Results

Electrocardiographic findings: Table II summarizes the electrocardiographic findings and type of ar-

TABLE II

Electrocardiographic Data and Previously Documented Arrhythmias of 13 Patients

Case no.	P-R Interval	QRS Interval	+ LVH	+ Abnormal Q Waves	Left Axis Deviation*	Arrhythmias
1	0.18	0.08	+	0	0	APC, PVC, PSVT
2	0.16	0.08	+	...	...	APC, PVC, VT
3	0.18	0.08	0	+	+	APC, PVC
4†	0.20	0.12 (IVB)	...	+	+	APC, PVC, PSVT
5	0.16	0.08	0	0	0	APC, PVC, PSVT, VT
6	0.22	0.10	+	+	+	APC, PVC, PSVT, VT
7†	0.21	0.08	+	0	0	APC, PVC, PSVT, AF
8	0.18	0.08	0	0	0	APC, PVC, PSVT
9	0.16	0.08	+	0	0	APC, PVC, PSVT, VT
10	0.18	0.12 (RBBB)	+	0	0	APC, PVC
11	0.19	0.08	0	+	0	APC, PVC
12	0.16	0.08	+	0	0	PVC
13	‡	0.08	+	+	0	1° A-V block, Mobitz type I A-V block

* Axis greater than −30°.
† Electrocardiographic data are postoperative.
‡ Advanced second degree atrioventricular block.
AF = atrial fibrillation; APC = atrial premature complexes; A-V = atrioventricular; IVB = nonspecific intraventricular block; LVH = left ventricular hypertrophy according to Estes' criteria; PSVT = paroxysmal supraventricular tachycardia; PVC = premature ventricular complexes; RBBB = right bundle branch block; VT = ventricular tachycardia; + = present; − = absent.

TABLE III

Resting Intracardiac Conduction Intervals in 13 Patients

Case no.	Atrial Cycle Length (msec)	P-A (msec)	A-H (msec)	H-V (msec)	Cycle Length of Atrial Pacing Producing Mobitz Type I Block (msec)
1	785	35	100	60	<380
2	940	35	90	55	380
3	790	30	90	70	530
4	920	30	112	60	380
5	860	40	75	60	<430
6	690	25	115	80	<430
7	1135	20	125	65	<400
8	650	25	65	55	<400
9	1060	25	90	45	390
10	1015	40	90	65	380
11	800	20	110	50	500
12	725	40	85	60	375
13	1025	30	*	*	*
Mean	876	28.1	95.6	60.4	...
±SEM	±42.2	±1.9	±5.2	±2.7	...

* Patient with advanced second degree atrioventricular block (see text).
SEM = standard error of the mean.

rhythmias found in the 13 patients. At the time of electrophysiologic study, two patients had a prolonged P-R interval (greater than 200 msec) and two had a prolonged QRS interval. No patient had evidence of ventricular preexcitation. Eight patients had left ventricular hypertrophy. Abnormal Q waves were present in 4 of the 11 patients who had not had previous surgery, and a mean QRS axis of −30° or less was present in 2 of these 4 patients. Eleven patients showed both atrial and ventricular premature complexes when evaluated with ambulatory monitoring, and seven had episodes of paroxysmal supraventricular tachycardia during such monitoring. Cycle lengths during tachycardia ranged from 325 to 525 msec, and all episodes were preceded by atrial premature complexes. Most episodes were of short duration and all were asymptomatic. In some instances (Patients 5 and 7) 2:1 A-V block occurred during tachycardia and P waves could be identified, but in the others the P waves could not be distinguished. Four patients had previously experienced brief episodes of self-terminating ventricular tachycardia. At the time of the study, one patient (Case 13) had complete A-V block with a narrow QRS complex; his previous electrocardiograms had shown Mobitz type I block.

Intracardiac conduction intervals and atrial pacing: Resting cycle lengths and conduction intervals are summarized in Table III. The P-A and A-H intervals were within normal limits in the 12 patients with intact A-V conduction. The H-V interval was normal in only 2 of the 12 patients in whom it could be measured. In Patient 13, who had complete heart block and a narrow QRS complex, a His bundle electrogram could not be

TABLE IV

Refractory Period Determination During Atrial Pacing in 11 Patients

Case no.	ERP_{at} (msec)	ERP_{avn} (msec)	FRP_{avn} (msec)
1	230	305*; <285	400*; 440
2	305	420*; <380	500*; 580
3	320	450*; 395	515*; 580
4	250	320	400
5	300	<320	<410
6	260	<320	480
7	205	<310	420
8	300	<345	365
9	240	280	410
10	275	375*; 350	500*; 475
11	220	420	540
12	420	<490†	<490

* When two values for refractory period are listed, the first represents a "fast" and the second a "slow" pathway of the atrioventricular (A-V) node. See text.

† A dual response developed after propranolol (see Table V).

Statistical evaluation performed using Student's t test for paired data.

ERP_{avn} = effective refractory period of the A-V node; ERP_{at} = effective refractory period of the atrium; FRP_{avn} = functional refractory period of the A-V node.

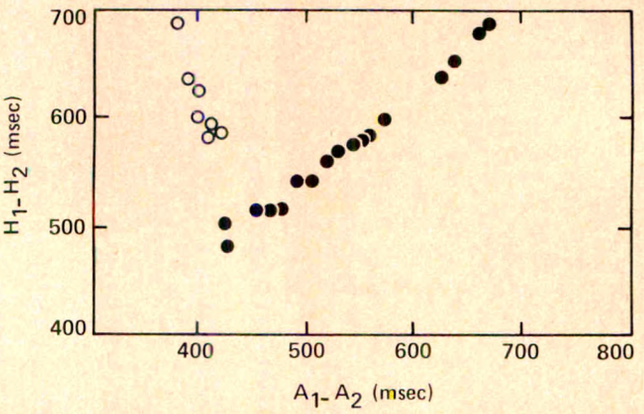


FIGURE 1. Case 2. Refractory curve of the atrioventricular (A-V) node obtained with the extrastimulus technique, suggesting dual A-V nodal pathways. The **closed circles** represent conduction through a "fast" pathway, and the **open circles** conduction through a "slow" pathway with a shorter effective refractory period than that of the fast pathway. At an A_1-A_2 interval of 425 msec, conduction occurred either through the fast pathway, with an H_1-H_2 interval of 495 msec, or through the slow pathway, with an H_1-H_2 interval of 580 msec. At A_1-A_2 intervals of 420 msec and less, conduction occurred exclusively through the slow pathway.

recorded. The atrial cycle length was regular at 1,025 msec, and the ventricular cycle length was regular at 1,735 msec. Atropine decreased the atrial cycle length to 940 msec and decreased the ventricular cycle length to 1,220 msec, still without an apparent relation between atrial and ventricular activity.

Atrial pacing at increasingly faster rates resulted in Mobitz type I A-V nodal block at an abnormally long cycle length (greater than 430 msec) in 2 of the 12 patients tested.

Refractory periods: Atrial and A-V nodal refractory periods were determined during atrial pacing in 12 patients (Table IV). The mean atrial effective refractory period was 277 msec and exceeded 300 msec in 3 of the 12 patients. In seven patients the atrial functional refractory period exceeded the effective refractory period, precluding determination of the latter. However, the effective refractory period of the A-V node was prolonged in three of the remaining five patients (Cases 3, 10 and 11). Relative refractory periods of the distal specialized conduction system during sinus rhythm were determined in two patients (Cases 2 and 7) and were normal.

TABLE V

A-V Nodal Refractory Periods Before and After Propranolol in Patients with Dual A-V Nodal Physiology (in msec)

Case no.	ERP		FRP	
	C	P	C	P
1	305; 285	300; 275	400; 440	385; 480
2	420; <380	505; <425	500; 580	590; 620
3	450; 395	465; <440	515; 580	540; 595
6	<320	400; <385	480	510; 610
8	<345	320; <285	365	370; 440
10	375; 350	—	475; 500	—
12	<490	325; 295	<490	440; 420

— = refractory periods determinations not made.

C = control; ERP = effective refractory period; FRP = functional refractory period; P = propranolol.

Dual A-V nodal pathways (Table V): In four patients (Cases 1, 2, 3 and 10) it was clear that dual A-V nodal refractory periods existed before propranolol was administered (see Tables IV and V and Fig. 1). This feature of A-V nodal conduction has previously been interpreted as reflecting a "fast" and a "slow" physiologic response of the A-V node to atrial extrastimuli.[13,14] Two of the four patients with this A-V nodal response had previously documented supraventricular tachycardia on ambulatory monitoring. Evidence of dual conduction pathways was uncovered after the administration of propranolol in an additional three patients (Cases 6, 8 and 12), two of whom had documentation of supraventricular tachycardia (see below). Thus, 7 of the 12 patients tested had evidence of dual A-V nodal pathways.

Effects of propranolol: Propranolol administration resulted in significant increases in mean atrial cycle length and mean A-H interval. The P-A and H-V intervals did not change significantly after propranolol. The atrial cycle length at which Mobitz type I block occurred was compared before and after administration of propranolol in six patients and tended to be longer after propranolol, but the difference was not significant.

The effect of propranolol upon A-V nodal conduction during atrial extrastimulation was determined in 11 patients. Three patients (Cases 6, 8 and 12) demonstrated dual A-V nodal responses *only after* propranolol had been administered (Table V). In two of these three patients the atrial refractory periods shortened with propranolol, allowing evaluation of A-V nodal conduction characteristics at shorter A_1-A_2 intervals. In two patients (Cases 1 and 3) similar basic atrial pacing rates before and after propranolol allowed comparison of the effects of propranolol on the dual responses. In one patient the A-V nodal effective refractory period of the fast response increased, but in the other patient this response decreased. The functional refractory period of the fast response decreased after propranolol administration in one patient and increased in the other; the functional refractory period of the slow response increased in both patients. Propranolol did not abolish the dual response in any patient, as determined during sinus rhythm or atrial pacing, although postpropranolol determinations were not accomplished in one patient (Case 10) with a dual response.

Discussion

In this investigation we performed intracardiac electrophysiologic studies in a group of patients with obstructive idiopathic hypertrophic subaortic stenosis and documented arrhythmias. In addition, we determined the effects of propranolol upon conduction system physiology in these patients.

Intraatrial and atrioventricular conduction: Intraatrial conduction, as judged from the P-A interval, was normal in all 13 patients. Only one patient had significant prolongation of the atrial effective refractory period. Disturbances of A-V nodal electrophysiology were surprisingly common. Although all A-H interval values were normal, two patients manifested abnormally early Wenckebach conduction during progressively more rapid atrial pacing. When determinable, the effective refractory period was frequently prolonged. Patient 13 had a history of Mobitz type I block and, although this has been shown to occur at any level of the conduction system, the narrow QRS configuration observed during both Mobitz type I block and complete heart block and the patient's response to atropine favor the A-V node as the site of block. Tajik et al.[15] reported on a patient with idiopathic hypertrophic subaortic stenosis and nonsurgical heart block, but their patient, unlike our Patient 13, had a wide QRS complex and idioventricular rhythm. Johnson and Daily[16] recently reported on a patient with this disease and advanced second degree A-V block with a prolonged H-V interval, but the site of block was not clearly determined.

Dual A-V nodal responses: Seven of 12 of our patients (58 percent) demonstrated dual A-V nodal responses. In spite of persistent attempts, we were unable to precipitate tachyarrhythmias in these patients during electrophysiologic evaluation. However, five of these seven patients had supraventricular tachycardia previously documented on ambulatory electrocardiographic monitoring. Three patients had dual A-V nodal responses only after propranolol administration, raising the possibility that under certain circumstances propranolol could affect refractory periods in such a way as to allow reentry to occur. Propranolol did not abolish the dual response in any patient demonstrating it during the control evaluation period. These data suggest that if dual A-V nodal pathways account for the large incidence of supraventricular tachycardia in patients with idiopathic hypertrophic subaortic stenosis, this incidence might be increased rather than decreased by propranolol.

Denes and Rosen and their co-workers[13,14] suggested that "fast" and "slow" A-V nodal conduction pathways can be delineated with the atrial extrastimulus technique in certain patients and that these dual pathways allow a physiologic basis for reentrant supraventricular arrhythmias in the absence of A-V nodal bypass pathways. In some of their patients they demonstrated echo beats and precipitated reentrant supraventricular tachycardia while delivering stimuli in the refractory zone of the slow pathway. The frequency of this physiologic response of the A-V node in the general population, in patients with reentrant supraventricular tachycardia without preexcitation or other pathologic conditions, as well as the effects of drugs upon the phenomenon, remains to be determined.

His-Purkinje conduction: Ten of 12 of our patients (83 percent) had prolonged H-V intervals at rest, indicating a remarkably large incidence of prolonged His-Purkinje conduction in these patients. All 10 of these patients had previously documented premature ventricular complexes, and 2 had a frequency of more than 10 premature ventricular contractions per 1,000 sinus beats on ambulatory electrocardiographic monitoring. Three of the four patients with previously documented ventricular tachycardia had abnormal H-V intervals. It seems unlikely that this large incidence of conduction disease in the His-Purkinje system is a result of ventricular hypertrophy alone. Dhingra et al.[17] recently reported on the occurrence of H-V interval prolongation in aortic stenosis. Among patients with aortic stenosis and intact A-V conduction, they found a large incidence of H-V interval prolongation only in those who had aortic valve calcification. Their 10 patients with intact A-V conduction who had electrocardiographic left ventricular hypertrophy and absence of bundle branch block, but no aortic valve calcification, had uniformly normal H-V intervals. On the other hand, all of their patients who had had documented A-V block did have significant valve calcification. These findings suggest that ventricular hypertrophy alone, in the absence of valve calcification, does not produce H-V interval prolongation.

Cardiac arrhythmias: Relation to A-V nodal and distal conduction disease: It is clear that patients with idiopathic hypertrophic subaortic stenosis experience many arrhythmias that may not be appreciated as symptoms but that may play a significant role in morbidity and mortality.[1,2,6,10,11] Recently, James and Marshall[18] reviewed the pathologic findings in the conduction system of patients with this disease and

found a variety of cystic and vascular abnormalities involving the A-V node and His bundle, as well as a persistent infantile dispersion of the A-V node throughout the central fibrous body. Coltart and Meldrum[19] used micropuncture techniques to demonstrate electrophysiologic abnormalities in the abnormal myocardium typical of this disease. Partial explanations for the electrophysiologic responses that we found in the A-V node and distal conduction system may lie in these observations, and both the extent and distribution of these abnormalities may play a significant role in the arrhythmias and conduction abnormalities that a patient with idiopathic hypertrophic subaortic stenosis may experience. The large incidence of abnormalities in the distal specialized conduction system in our group of both medical and surgical patients has heretofore been unrecognized and has potentially important prognostic and therapeutic implications.

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Inferior Myocardial Infarction as a Cause of Asymmetric Septal Hypertrophy

An Echocardiographic Study

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The diastolic thickness of the septum and posterior left ventricular wall were measured with M mode echocardiography in 68 patients 2 or more months after a single transmural myocardial infarction. In 42 patients with inferior wall infarction, the septal thickness of 12.4 ± 0.6 mm (mean ± standard error of the mean) was larger than the mean measurement in 26 patients with anterior wall infarction (9.6 ± 0.6 mm, $P < 0.01$). Twenty-five of these 42 patients (59 percent) had increased septal thickness (greater than 11 mm), including 12 (48 percent) who had hypertension and 11 (26 percent) who had decreased posterior wall thickness. The ratio of septal to posterior wall thickness was greater in the patients with inferior infarction than in those with anterior infarction (1.36 ± 0.06 versus 0.89 ± 0.06, $P < 0.001$). This ratio exceeded 1.3 in 22 patients with an inferior infarction (52 percent) but was increased in only 1 patient with an anterior infarction. Hypertension did not predict the presence or absence of an abnormal ratio. Increased septal thickness on echocardiography may occur after inferior infarction and result in an abnormal septal to posterior wall thickness ratio that meets current echocardiographic criteria for asymmetric septal hypertrophy.

Asymmetric septal hypertrophy as detected noninvasively with echocardiography has been suggested as the primary abnormality in patients with hypertrophic cardiomyopathy with or without left ventricular outflow tract obstruction. The characteristic echocardiographic abnormality is an interventricular septal to posterior left ventricular diastolic wall thickness ratio greater than 1.3.[1–4] However, an increase in this ratio has been described recently in adults with right ventricular pressure overload,[5,6] normal children[7] and children with congenital heart disease.[6–10] Two recent reports[11,12] indicate that disproportionate septal thickening on echocardiography may also occur in professional athletes with "physiologic" left ventricular hypertrophy. Ischemic heart disease and myocardial infarction frequently result in altered segmental left ventricular function and regional left ventricular wall thickness abnormalities.[13–19] Such distortions in left ventricular geometry late after myocardial infarction may result from regional or generalized left ventricular dilatation, atrophy of infarcted myocardium and compensatory hypertrophy of myocardial tissue in noninfarcted areas of the left ventricle. Alterations in septal and left ventricular posterior wall thickness measurements in patients with previous myocardial infarction may lead to abnormalities in the thickness ratio of these two structures. We therefore examined the influence of previous myocardial infarction on ultrasonic measurements of interventricular septal and left ventricular posterior wall thickness and compared the results with currently available echocardiographic criteria for asymmetric septal hypertrophy.

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Methods

Patients: The study group consisted of 54 men and 14 women whose mean age was 57 years (range 35 to 76). In all 68 patients, a single transmural myocardial infarction was diagnosed with use of the following criteria: (1) a history of typical prolonged chest pain, (2) electrocardiographic changes indicative of acute myocardial injury with the subsequent evolution of a typical transmural infarction pattern, and (3) characteristic elevations of serum enzymes (creatine kinase [CK], glutamic oxaloacetic transaminase [GOT], lactic dehydrogenase (LDH]). All 68 patients were studied consecutively in the Myocardial Infarction Research Unit as part of regular routine follow-up examinations 2 to 68 months after an acute myocardial infarction (average 26 months). The initial study group consisted of 80 consecutive patients with a single previous transmural myocardial infarction; 12 of these (15 percent) were excluded because they had echocardiograms unsatisfactory for measurement of ventricular wall thickness. No patient had historical or electrocardiographic evidence of another myocardial infarction and none had a recurrent infarction between the initial event and the time of study.

The electrocardiogram revealed an inferior wall infarction in 42 patients, including 4 with additional lateral wall and 4 with additional posterior wall involvement. The remaining 26 patients had anterior wall infarction as judged from the electrocardiogram, and 12 of these also had lateral wall involvement. Twenty-five patients had documented systemic hypertension before or after myocardial infarction, or both. This diagnosis was based on elevated blood pressure measurements obtained on at least two separate occasions of 160 mm Hg or more systolic or 95 mm Hg or more diastolic, or both. Twenty-three had documented elevated blood pressure before acute myocardial infarction, and 17 of these had persistent hypertension after infarction that required drug therapy. In two patients hypertension was documented for the first time after infarction. Thus, 15 of the 42 patients (36 percent) with inferior infarction and 10 of the 26 patients (38 percent) with anterior infarction were considered to have hypertension.

Echocardiographic dimensions: Echocardiograms were obtained using a Picker Echoview II, utilizing a 2.25 megahertz, 1.25 cm transducer focused at 7.5 cm, or a 1.6 megahertz, 1.9 cm transducer focused at 10 cm. The output of the ultrasonoscope was recorded simultaneously with lead II of the electrocardiogram on a Honeywell Visicorder Oscillograph model no. 1856 at a paper speed of 50 or 100 mm/sec. The patients were studied in the left lateral decubitus position during normal respiration. The transducer was positioned close to the left sternal border in the third, fourth and fifth intercostal spaces sequentially with the ultrasonic beam directed posteriorly and slightly medially until the echogram of the anterior leaflet of the mitral valve was identified. The transducer was then directed inferolaterally until the echoes from the endocardial surface of the interventricular septum and the posterior left ventricular wall could clearly be identified at the level of the chordae tendineae (Fig. 1). By careful adjustment of the gain and reject controls a clear image of the echoes was obtained. In each study increased damping during recording was used to identify accurately the pericardial and epicardial surfaces of the left ventricular posterior wall.

The left ventricular internal end-diastolic dimension was measured between endocardial surfaces along the vertical line through the peak of the QRS complex. Both septal and posterior left ventricular wall thicknesses were measured during ventricular diastole before the P wave of the electrocardiogram. Measurements of ventricular septal thickness were made between the anterior edges of the right and left ventricular septal endocardial surfaces (leading edge to leading edge) to the nearest 0.5 mm (Fig. 1). Similarly, thickness of the left ventricular posterior wall was measured from the anterior edge of the endocardium to the anterior edge of the epicardial surface of the posterior wall (Fig. 1). All measurements were obtained using the average of three beats. In our laboratory the normal limits for diastolic septal thickness are 7.8 to 11.0 mm and for diastolic posterior wall thickness 7.6 to 11.0 mm. The ratio of ventricular septal to left ventricular posterior wall thickness also was calculated in each patient. Previously described echocardiographic criteria for asymmetric septal hypertrophy were used, and a ratio of septal to posterior wall thickness equal to or exceeding 1.3 was considered abnormal.[1,2]

Statistical analysis: All measurements were made by one observer who was unaware of the electrocardiographic site of infarction, and all data were analyzed using standard statistical methods with the aid of a Sigma III computer. To eval-

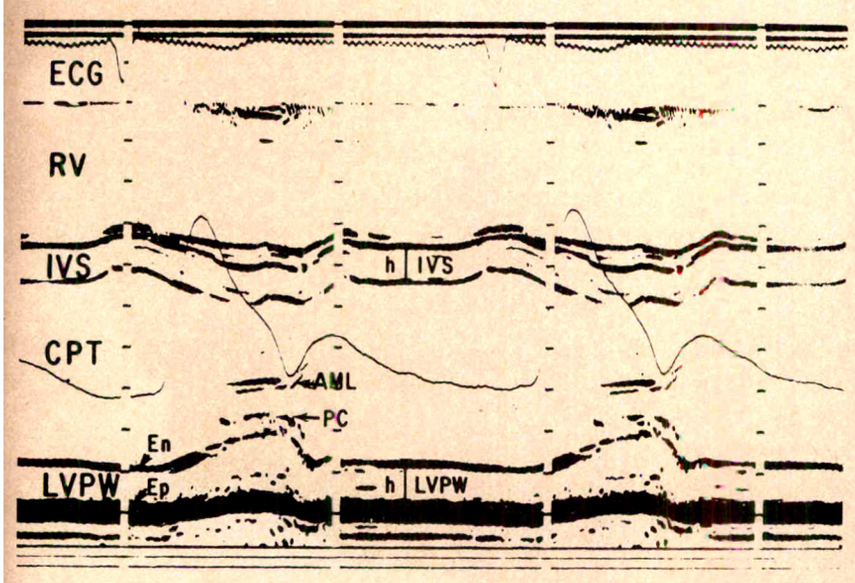


FIGURE 1. Echocardiogram showing the interventricular septum (IVS) and the free left ventricular posterior wall (LVPW) with the ultrasonic beam traversing the left ventricular wall in a perpendicular fashion at the level of the chordae tendineae. Time-distance markers and a carotid arterial pulse tracing (CPT) are incorporated in the tracing. AML = anterior mitral valve leaflet; ECG = electrocardiogram; En = the leading edge of the posterior wall endocardium; Ep = leading edge of the posterior wall epicardium; h IVS = septal thickness; h LVPW = left ventricular posterior wall thickness; PC = posterior chordae; RV = right ventricle. For details of measurements, see text.

uate interobserver variation, measurements were made from 15 randomized echocardiographic tracings by a second observer and statistically compared using a paired Student's *t* test and statistical analysis for reliability of the measurements.[20] There was good agreement between the two observers' measurements ($r = 0.96$ for septal thickness, $r = 0.90$ for left ventricular posterior wall thickness), and the largest interobserver difference was 1.0 mm for septal thickness and 1.5 mm for posterior wall thickness. The coefficient for reliability of the measurement was 0.89.

Results

Ventricular septal thickness (Fig. 2): In the 42 patients with an inferior wall infarction, the mean ventricular septal thickness was 12.4 ± 0.6 (standard error of the mean) mm with a range of 7.5 to 22.9. This was significantly greater ($P < 0.005$) than the mean septal thickness in the 26 patients with anterior wall infarction (9.6 ± 0.6 mm with a range of 3.6 to 18.6). Septal thickness was increased (greater than 11 mm) in 25 of the 42 patients (59 percent) with inferior infarction and 12 of these patients had hypertension; septal thickness was increased in 8 of 26 patients (31 percent) with anterior infarction, and 5 of these 8 had hypertension. A decreased septal thickness (less than 7.8 mm) was found in six patients (23 percent) with anterior infarction and in only one patient with inferior infarction.

Posterior wall thickness (Fig. 3): Left ventricular posterior wall thickness averaged 9.4 ± 0.4 mm (range 5.1 to 17.3 mm) in the 42 patients with prior inferior infarction. This value was significantly lower than that in the 26 patients with anterior infarction (mean 11.0 ± 0.5 mm; range 7.3 to 15.8) ($P < 0.02$). Ten of the 42 patients (24 percent) with inferior infarction had increased posterior wall thickness (greater than 11 mm) and 6 of these had hypertension. Eleven of the 42 patients (26 percent) with inferior infarction had decreased posterior wall thickness (less than 7.6 mm). Thirteen of the 26 patients (50 percent) with anterior infarction had increased posterior wall thickness and 6 of these patients had hypertension.

Ratio of septal to posterior wall thickness (Fig. 4): In the 42 patients with inferior infarction, the mean

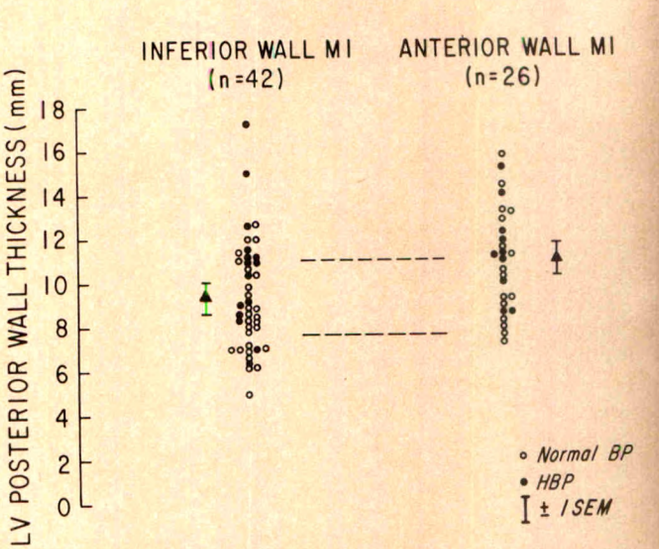


FIGURE 3. Individual measurements and group mean values of left ventricular (LV) posterior wall thickness in patients with prior inferior transmural infarction (MI) and in patients with anterior infarction. The **dashed lines** depict the normal ranges between 7.6 and 11.0 mm for posterior wall thickness. BP = blood pressure; HBP = hypertension; SEM = standard error of the mean.

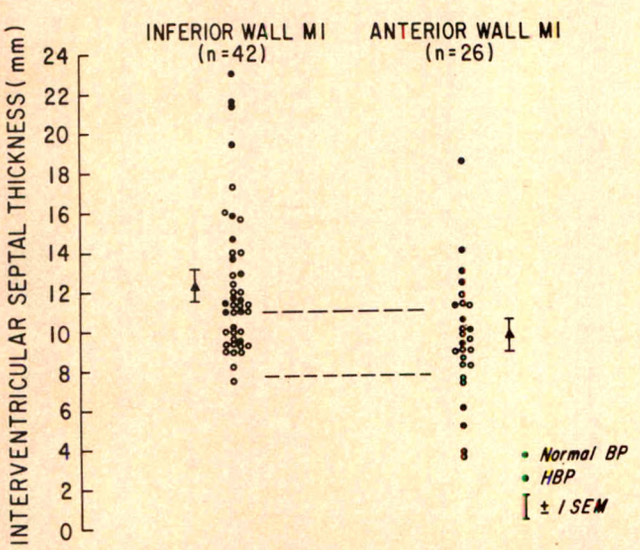


FIGURE 2. Measurements of interventricular septal thickness and the group mean values are shown for 42 patients with a prior isolated inferior transmural myocardial infarction (MI) and for 26 patients with a prior anterior wall infarction. The **dashed lines** indicate the normal limits of septal thickness ranging between 7.8 and 11.0 mm. BP = blood pressure; HBP = hypertension; SEM = standard error of the mean.

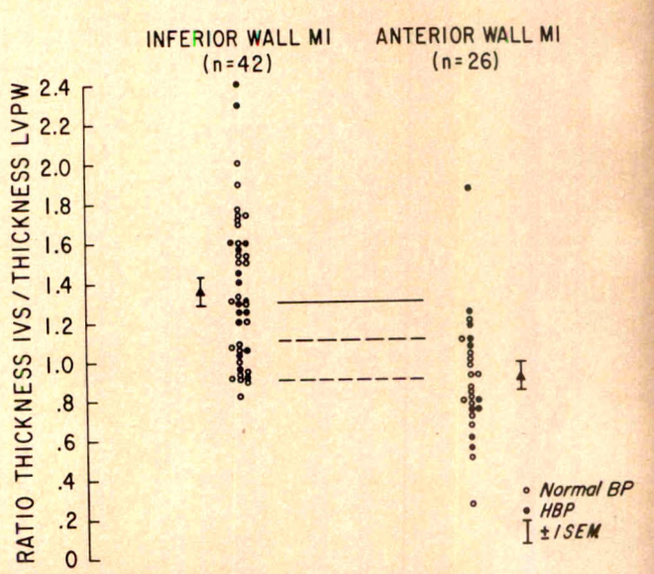


FIGURE 4. Individual measurements and group mean values of septal to left ventricular posterior wall (LVPW) thickness ratios in patients with prior transmural myocardial infarction. The **dashed lines** indicate the normal range (0.9 to 1.12) for the septal to posterior wall ratio and the **solid line** the value of 1.3. BP = blood pressure; HBP = hypertension; SEM = standard error of the mean.

ventricular septal to left ventricular posterior wall thickness ratio was 1.36 ± 0.06 (range 0.82 to 2.4). This value was significantly higher than that in the 26 patients with previous anterior infarction where mean ratio was 0.89 ± 0.06 (range 0.25 to 1.86) (P <0.0001). The septal to posterior wall ratio in patients with inferior infarction exceeded 1.3 in 22 of 42 patients (52 percent).

Table I summarizes the echocardiographic measurements of the 23 patients whose septal to posterior wall ratio exceeded 1.3. The increased ratio in the 22 patients with prior inferior infarction was due to an increased septal thickness in 17 patients, including 8 with a normal, 5 with a decreased and 4 with an increased posterior wall thickness. In the remaining five patients with inferior infarction, the increased septal to posterior wall ratio was due to decreased posterior wall thickness with normal thickness of the septum. Only 1 of the 26 patients with anterior infarction had an increased ratio due to an increased septal and a normal posterior wall thickness. This patient had systemic hypertension. Two echocardiograms of the patients with an increased ratio studied late after transmural inferior myocardial infarction are illustrated in Figure 5.

TABLE I

Echocardiographic Measurements in 23 Patients With Myocardial Infarction and an Abnormal Interventricular Septal to Posterior Wall Thickness Ratio of 1.33 or More

ECG Infarct Site	IVS/LVPW Ratio	Thickness		LVEDD (mm)	Hypertension
		IVS (mm)	LVPW (mm)		
Inf	1.33	16.0	12.0	49	−
Inf	1.33	11.3	8.5	56	−
Inf, post	1.37	10.0	7.3	48	−
Inf	1.39	15.9	11.4	47	+
Inf	1.44	21.6	15.0	49	+
Inf, post	1.50	12.0	8.0	56	−
Inf	1.52	10.0	6.6	54	−
Inf, post	1.54	13.1	8.5	53	−
Inf	1.56	16.7	10.7	52	−
Inf	1.57	19.6	12.5	72	+
Inf	1.60	10.0	6.2	59	−
Inf	1.61	10.3	6.4	71	+
Inf	1.62	11.8	7.2	62	+
Inf	1.67	11.4	6.8	46	−
Inf, post	1.71	12.0	7.0	51	−
Inf	1.75	12.4	7.1	64	−
Inf	1.75	14.0	8.0	55	−
Inf	1.76	15.8	9.0	54	−
Ant, lat	1.86	18.6	10.0	52	+
Inf	1.90	9.7	5.1	53	−
Inf, lat	2.02	14.0	6.9	49	−
Inf	2.34	21.6	9.2	56	+
Inf, lat	2.40	22.9	9.5	54	+

− = absent; + = present.

Ant = anterior; ECG = electrocardiographic; Inf = inferior; IVS = interventricular septum; lat = lateral; LVEDD = left ventricular end-diastolic dimension; LVPW = left ventricular posterior wall; post = posterior.

Wall thickness measurements in patients with coexisting hypertension: The 15 hypertensive patients with inferior infarction had significantly larger septal thickness measurements than the 27 normotensive patients with inferior infarction (14.7 ± 0.1 versus 11.2 ± 0.05 mm, P <0.01). Similarly, patients with inferior infarction and hypertension had significantly greater posterior wall thickness measurements than those without hypertension (10.6 ± 0.07 versus 8.7 ± 0.04 mm, P <0.02). However, the mean septal to posterior wall ratio in patients with prior inferior infarction was not different when the patients with hypertension were compared with normotensive patients (1.42 ± 0.07 versus 1.33 ± 0.1).

Among patients with anterior infarction, the mean septal thickness in the 10 patients with hypertension was significantly greater than in the 16 patients without hypertension (11.1 ± 0.1 versus 8.6 ± 0.06 mm, P <0.05). The mean posterior wall thickness in patients with anterior infarction was not significantly different in hy-

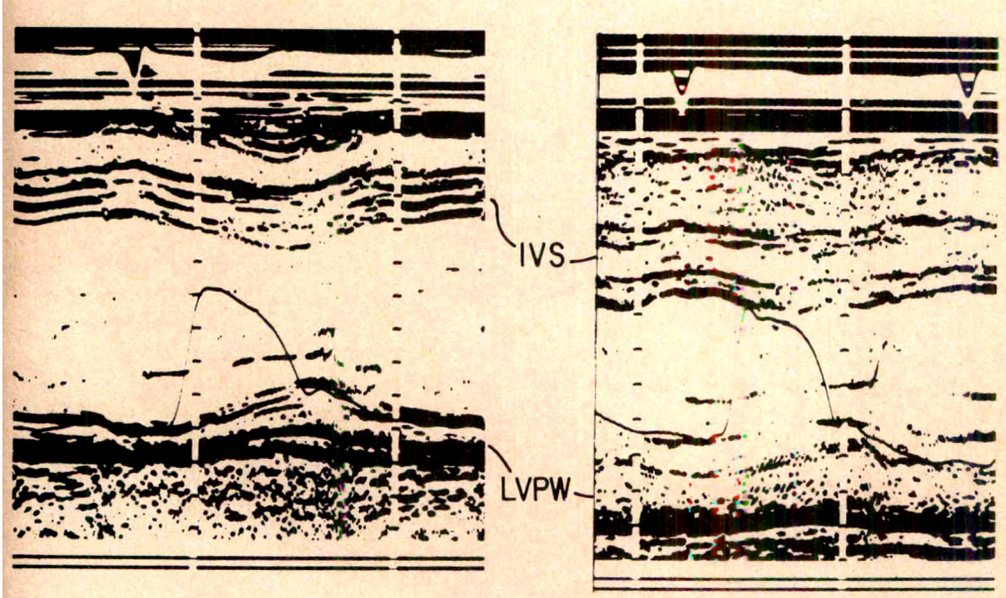


FIGURE 5. Echocardiograms in two patients studied late after transmural inferior wall infarction. **Left,** a 69 year old man with chronic left ventricular failure 30 months after acute inferior myocardial infarction. The increased septal (IVS) thickness of 12.4 mm and a thin posterior left ventricular wall (LVPW) of 7.1 mm result in an increased septal to posterior wall ratio of 1.75. The end-diastolic dimension is greatly enlarged. **Right,** a 51 year old man with longstanding hypertension and chronic congestive heart failure 24 months after inferior myocardial infarction. The increased septal (21.6 mm) and posterior wall thicknesses (15 mm) resulted in a septal to posterior wall ratio of 1.44.

pertensive and normotensive patients (11.4 ± 0.07 mm versus 10.7 ± 0.06 mm). Also, the mean septal to posterior wall ratio of 0.99 ± 0.12 in patients with anterior infarction and hypertension was not different from the mean ratio of 0.83 ± 0.06 in patients with anterior infarction without hypertension.

Discussion

Our data indicate that in patients with a single inferior myocardial infarction increased thickness of the septum is common and may result in an increase in the septal to posterior wall thickness ratio that often meets the current echocardiographic criteria for asymmetric septal hypertrophy. The greater septal to posterior wall ratio in 22 of the 42 patients with previous inferior wall infarction and in 1 of the 26 patients with a prior anterior wall infarction was associated with increased septal thickness in the majority (78 percent) of cases. However, a posterior wall thickness measurement of less than 7.6 mm was present in 10 of the 23 patients with an elevated septal to posterior wall ratio, and in 5 patients the increased ratio was caused solely by the thin left ventricular posterior wall. A thin posterior wall was present in patients who had either additional electrocardiographic evidence of infarction of the posterior and lateral walls or an enlarged left ventricular end-diastolic dimension on echocardiography (Table I). It is possible that scarred posterior wall myocardium was traversed by the standard ultrasonic beam in patients with a previously infarcted posterior wall, thus accounting for the thin wall measured late after myocardial infarction. Conversely, overall or regional left ventricular dilatation could have produced a thin posterior wall because changes in wall thickness can occur with reciprocal changes in left ventricular chamber size.[21] The disproportionate ventricular septal thickness associated with a thin posterior wall in our patients, who had no clinical evidence of hypertrophic cardiomyopathy, appears to be similar to the reported findings in some patients with hypertrophic cardiomyopathy whose left ventricular free wall behind the posterior mitral leaflet is of less than normal thickness.[3,22]

Echocardiographic findings in inferior infarction versus hypertrophic cardiomyopathy: Others[4,23] have proposed that a septal to posterior wall ratio of 1.6 is more specific for the ultrasonic diagnosis of hypertrophic cardiomyopathy than is the ratio of 1.3. Our data indicate that a ratio over 1.6 may increase diagnostic specificity for this syndrome, but a considerable number of patients (26 percent) with inferior infarction would still meet such criteria. In addition, hypokinesia of the septum with reduced septal thickening and decreased septal excursion is a common echocardiographic finding in patients with hypertrophic cardiomyopathy.[24,25] A similar septal abnormality also was observed in 14 of our 20 patients who exhibited increased septal thickness and an abnormal septal to posterior wall ratio after myocardial infarction. Such septal abnormalities could be the result of clinically undetected coronary arterial obstruction in vessels supplying the interventricular septum.[26] Of these 14 patients, 7 (50 percent) had a diastolic septal thickness measurement exceeding 15 mm. Systolic anterior motion of the anterior mitral valve leaflet, which is common in hypertrophic cardiomyopathy with left ventricular outflow obstruction, also has been described in patients with left ventricular aneurysm after myocardial infarction.[27] Thus, echocardiographic abnormalities of the septum and anterior mitral valve leaflet typically seen in hypertrophic cardiomyopathy may also occur after transmural myocardial infarction and lead to difficulties in echocardiographic interpretation.

Although hypertrophic cardiomyopathy can be associated with obstructive coronary artery disease, there was no clinical evidence of the former condition in our patients with previous myocardial infarction and in none did provocative maneuvers elicit the typical murmur of hypertrophic cardiomyopathy. Twelve patients underwent cardiac catheterization within 2 months of the ultrasonic study and all 12 had obstructive coronary artery disease with more than 75 percent narrowing of luminal diameter of one or more vessels. Furthermore, echocardiographic evidence of systolic anterior motion of the anterior mitral valve leaflet was not demonstrated in these patients. Five of the seven patients with prior inferior infarction had a septal thickness measurement of more than 12 mm on echocardiography and four of these five patients also had a septal to posterior wall ratio over 1.3, but none had a pressure gradient across the left ventricular outflow tract.

Role of regional ventricular wall thinning: Abnormalities in regional wall thickness were detected in 73 percent of our patients. A septal thickness of less than 7.8 mm was measured in 23 percent of the patients with anterior infarction but in only 2 percent of those with inferior infarction. Similarly, a thin left ventricular posterior wall was measured in 26 percent of the patients with inferior infarction but in only 4 percent of those with anterior infarction. Corya et. al.,[16–18] observing an abnormal wall thickness in patients with coronary arterial obstruction and previous myocardial infarction, demonstrated a relation between thin septal areas, electrocardiographic site of infarction and histologically confirmed scar tissue. Similar results were demonstrated in experimental studies.[13,15,28] Thus, the echocardiographic visualization of a thin left ventricular wall may be helpful in identifying the location of a prior infarction.

Role of hypertension: Increases in both septal and posterior wall thickness measurements are common in patients with systemic hypertension.[29,30] The extent to which systemic arterial hypertension contributes to the increased wall thickness in patients with previous myocardial infarction remains unclear. In our study, patients with documented hypertension tended to have larger septal and posterior wall thickness measurements than normotensive patients with the same infarct site, but these differences were statistically significant only in patients with inferior infarction. However, the septal to posterior wall ratios did not differ between hypertensive and normotensive patients, suggesting that the

increased ratios observed in many of these postinfarction patients were not influenced by chronic systemic hypertension. This finding is in contrast to the left ventricular hypertrophy observed in hypertensive patients[31] with[29] and without[30] congestive heart failure, in whom a symmetrically thickened septum and left ventricular posterior wall can be demonstrated with ultrasound.

Implications: Our data indicate that the diagnosis of hypertrophic cardiomyopathy as established with echocardiography should be made cautiously in patients with previous inferior myocardial infarction. The ratio of the interventricular septum to the free left ventricular posterior wall appears to be a function of many variables, only one of which is the asymmetric septal hypertrophy of hypertrophic cardiomyopathy.

Acknowledgment

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Early Systolic Closure of the Aortic Valve in Patients With Hypertrophic Subaortic Stenosis and Discrete Subaortic Stenosis

Correlation with Preoperative and Postoperative Hemodynamics

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Patterns of motion of the aortic valve were analyzed with echocardiography in 9 patients with discrete subaortic stenosis and 31 patients with idiopathic hypertrophic subaortic stenosis, 22 with and 9 without a resting intraventricular pressure gradient. The intention was to determine whether the early systolic closure of the aortic valve was a sensitive indicator of a resting pressure gradient across the left ventricular outflow tract. All 9 patients with discrete subaortic stenosis and the 22 patients with idiopathic hypertrophic subaortic stenosis with a resting pressure gradient showed early systolic closure of the aortic valve; however, the 9 patients without a resting gradient had normal motion of the aortic valve. Measured values for O-ESC (the interval from the opening point of the aortic valve to the point of early systolic closure of the aortic valve) in 9 patients with discrete subaortic stenosis and in 22 with idiopathic hypertrophic subaortic stenosis averaged 0.05 ± 0.01 (standard deviation) second and 0.14 ± 0.04 second for each group, respectively ($P < 0.01$). Twelve patients with idiopathic hypertrophic subaortic stenosis underwent operation to alleviate left ventricular outflow tract obstruction. In eight of these patients the resting pressure gradient was completely abolished and early systolic closure of the aortic valve was no longer present. The results indicate that in idiopathic hypertrophic subaortic stenosis, early systolic closure of the aortic valve is recorded only when there is a significant intraventricular pressure gradient at rest. The time of occurrence of early systolic closure differentiated patients with discrete subaortic stenosis from those with idiopathic hypertrophic subaortic stenosis in all observations.

The first echocardiogram of the aortic valve was recorded in 1961.[1] Subsequently, examples of normal and diseased aortic valves were described.[2,3] Early to mid systolic closure of the aortic valve and fluttering of the cusps were reported in patients with idiopathic hypertrophic subaortic stenosis,[4–8] and a similar echocardiographic pattern was described in patients with discrete subaortic stenosis.[9–14] To our knowledge, however, the ultrasonic characteristics of the aortic valve in these two conditions have not been quantitatively compared.

The purpose of this study was to elucidate and emphasize further the specific echocardiographic patterns of motion of the aortic valve in patients with idiopathic hypertrophic subaortic stenosis and discrete subaortic stenosis and to establish criteria for differentiating the two entities. Although several echocardiographic studies[15–17] reported a relation between abnormal systolic anterior motion of the mitral valve and the presence of a subvalve gradient in idiopathic hypertrophic subaortic stenosis, few comparative data are available on aortic valve motion. Therefore, we also attempted to determine whether motion of the aortic valve in the echocardiogram correlated with the presence or

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TABLE I

Echocardiographic Changes Before and After Operation in Nine Patients With Discrete Subaortic Stenosis

Case no.	Age (yr) & Sex	LV Gradient At Rest (mm Hg) Preop	Early Systolic Closure of Aortic Valve	
			Preop	Postop
1	17M	45	Yes: RCC, NCC	Yes: NCC
2	34F	60	Yes: RCC	No
3	33M	85	Yes: RCC	Yes: NCC
4	56M	100	Yes: RCC	Yes: NCC
5	27M	60	Yes: RCC	—
6	16F	98	Yes: RCC	—
7	31F	90	Yes: RCC	—
8	47F	100	Yes: RCC	Yes: RCC
9	35M	60	Yes: RCC, NCC	Yes: RCC, NCC

LV = left ventricular; NCC = noncoronary cusp; Postop = postoperatively; Preop = preoperatively; RCC = right coronary cusp.

absence of a resting intraventricular pressure gradient in patients with idiopathic hypertrophic subaortic stenosis. Such a correlation would be helpful in assessing this disorder, particularly when various factors preclude the use of mitral valve motion as an indicator of obstruction.

Methods

Patients: Nine patients were diagnosed as having discrete subaortic stenosis on the basis of hemodynamic and angiographic data (Table I).[18] One of these patients also had cineangiographic evidence of idiopathic hypertrophic subaortic stenosis. There were five men and four women whose ages ranged from 16 to 56 years. All nine patients underwent preoperative echocardiography, and six who underwent surgical excision of the subaortic membrane also had postoperative echocardiograms.

Thirty-one patients had typical hemodynamic[19] and echocardiographic[17,20] features of idiopathic hypertrophic subaortic stenosis. Nine of these had a systolic intraventricular pressure gradient only after pharmacologic provocation with sublingual nitroglycerin.[21] Twenty-two patients (13 men and 9 women aged 16 to 69 years) had a resting gradient of 20 to 165 mm Hg (average 80). Of the 22 patients, 12 underwent various surgical procedures for relief of the left ventricular outflow tract obstruction (Table II). After operation, the 12 underwent hemodynamic, angiographic and echocardiographic reevaluation.

Echocardiographic studies: Echocardiograms were recorded under resting basal conditions within 24 hours of cardiac catheterization in all patients; no recording was obtained during catheterization. The echocardiographic studies were performed using a Smith Kline Ekoline 20 echograph with a 2.25 megahertz transducer focused at 7.5 cm or a 1.9 megahertz transducer focused at 10 cm. Simultaneous electrocardiographic, phonocardiographic and echocardiographic recordings were made with an IREX 101 multichannel recorder. The aortic valve echocardiograms were obtained with methods previously described.[1–4] Cardiac medications were discontinued before the study. Most recordings were made with the patient in the left lateral position and with the transducer applied to the fourth left intercostal space. An adequate echocardiogram of the aortic valve was defined as one in which there was visualization of both aortic cusps during the entire systolic period.

The following observations and measurements of the aortic valve were recorded (Fig. 1): (1) the presence or absence of early systolic closure of the aortic valve; (2) fluttering of the aortic cusps; (3) the presence or absence of high density, thin echoes in the left ventricular outflow tract in patients with discrete subaortic stenosis[10,13,14]; (4) the interval from the beginning of the Q wave of the surface electrocardiogram to the point of opening (O) of the aortic valve (Q-O interval); (5) the interval from the Q wave of the electrocardiogram to the point of maximal early systolic closure of the aortic valve (Q-ESC interval); (6) the interval from the opening point of the aortic valve to the point of maximal early systolic closure of the aortic valve (O-ESC), (7) left ventricular ejection time

TABLE II

Echocardiographic Changes Before and After Operation in 12 Patients With Idiopathic Hypertrophic Subaortic Stenosis

Case no.	Age (yr) & Sex	Early Systolic Closure of Aortic Valve		LV Gradient at Rest (mm Hg)		Type of Surgery
		Preop	Postop	Preop	Postop	
1	60F	Yes	No	160	0	MVR
2	30M	Yes	No	78	0	MVR
3	69F	Yes	No	120	0	MVR
4	21M	Yes	No	20	0	SM
5	16M	Yes	Yes	60	22	SM
6	62F	Yes	No	140	10	SM
7	61M	Yes	No	120	0	SM + MA with CR
8	51F	Yes	No	165	0	SM + PMV
9	42F	Yes	No	100	0	SM + MVR
10	23F	Yes	No	20	0	SM + MVR
11	31M	Yes	Yes	120	45	SM
12	28M	Yes	Yes	62	100	SM + CR

CR = Carpentier ring; LV = left ventricular; MA = mitral anuloplasty; MVR = mitral valve replacement with mitral prosthesis; PMV = porcine mitral heterograft; SM = septal myotomy and myomectomy.

(LVET) as determined from the opening to the closure of the aortic valve in the echocardiogram; and (8) the ratio of O-ESC to LVET. The probability (P) value was determined using Student's t test analysis.[22]

Results

Early systolic closure of the aortic valve in patients with discrete subaortic stenosis: Of the nine patients with this finding before operation, two had early systolic closure of both the right and noncoronary cusps, and seven had early systolic closure of the right coronary cusp alone (Fig. 1 and 2A). Of the six patients whose postoperative echocardiograms were available for study, five still manifested early systolic closure of one or both cusps. One patient (Case 2, Table I) had normal motion of both cusps; another (Case 1, Table I) had abnormal motion of the right coronary cusp only (Fig. 2B). The postoperative aortic valve echocardiogram showed no change in two patients. In two patients the right coronary cusp motion, previously abnormal, reverted to a normal pattern; however, the noncoronary cusp, normal before operation, demonstrated early systolic closure after operation. All nine patients with discrete subaortic stenosis showed notable fluttering of one or both cusps preoperatively. In five of six patients the fluttering persisted after operation. We were unable to detect any thin, high density echoes in the left ventricular outflow tract attributable to the subaortic membrane.

Early systolic closure of the aortic valve in patients with idiopathic hypertrophic subaortic stenosis: Nine patients without left ventricular outflow tract obstruction at rest did not have early systolic closure of the aortic valve. They were treated medically.

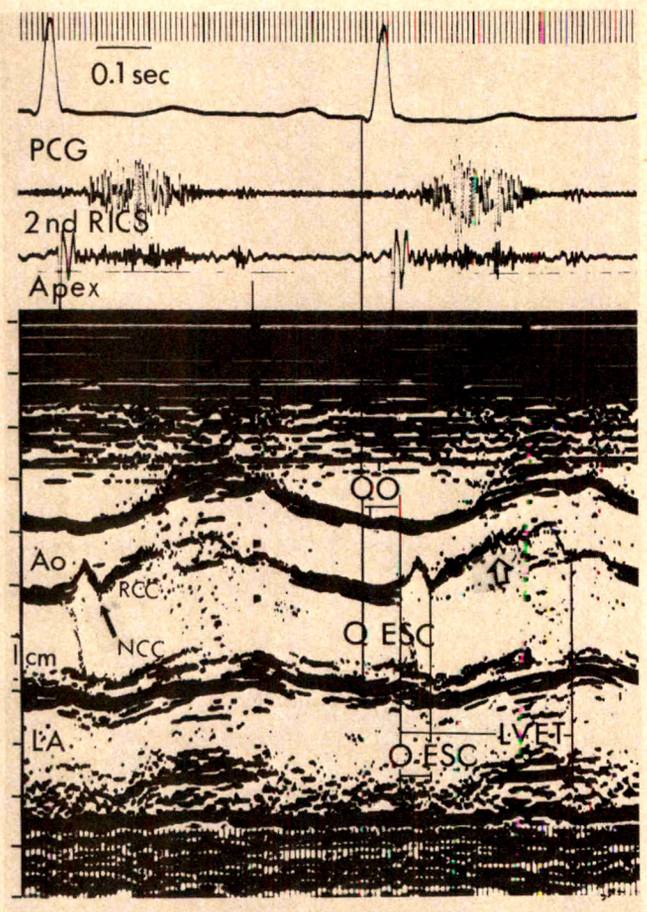


FIGURE 1. Case 9, Table I. Typical aortic valve echocardiogram of a patient with discrete subaortic stenosis. Early systolic closure **(solid arrow)** and fluttering **(open arrow)** are noted in both the noncoronary (NCC) and right coronary (RCC) cusps. Ao = aorta; LA = left atrium; LVET = left ventricular ejection time; O ESC = interval from point of opening of aortic valve to point of maximal early systolic closure; PCG = phonocardiogram; Q ESC = interval from Q wave to maximal early systolic closure of aortic valve; Q O = interval from Q wave to point of opening of aortic valve; RICS = right intercostal space.

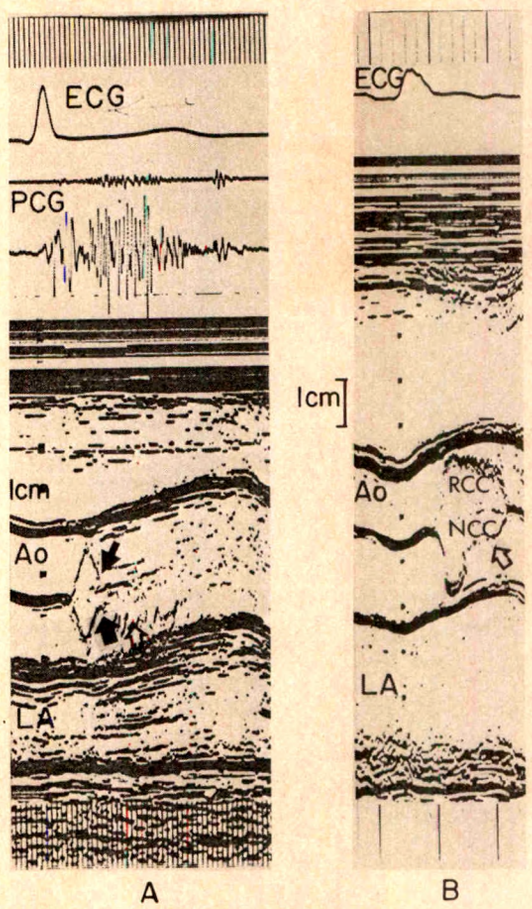


FIGURE 2. Case 1, Table I. Aortic valve echocardiogram of a patient with discrete subaortic stenosis. **A,** preoperatively, both aortic cusps **(solid arrows)** show early systolic closure 0.05 second after the valve begins to open. There is notable fluttering of the noncoronary cusp (NCC) during systole **(open arrow). B,** postoperatively, the right coronary cusp (RCC) opens normally, whereas the noncoronary cusp still shows early systolic closure **(arrow).** ECG = electrocardiogram; other abbreviations as in Figure 1.

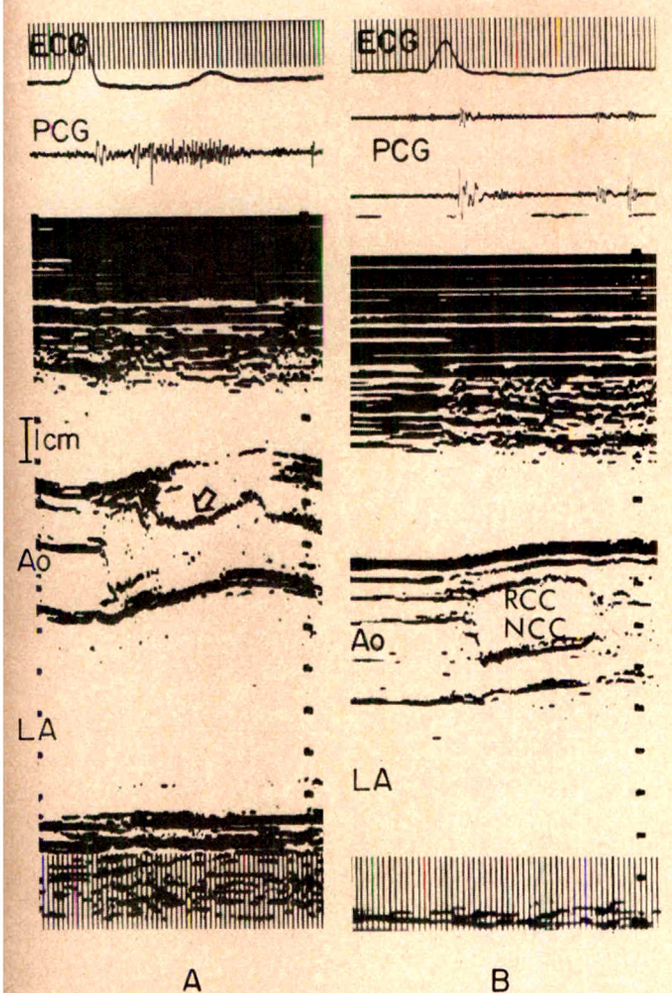


FIGURE 3. Case 2, Table II. Aortic valve echocardiogram of a patient with idiopathic hypertrophic subaortic stenosis. **A,** preoperatively, the right coronary cusp displays early systolic closure **(solid arrow at left of open arrow)** and fluttering **(open arrow). B,** postoperatively, the cusp remains open through systole. Abbreviations as in Figures 1 and 2.

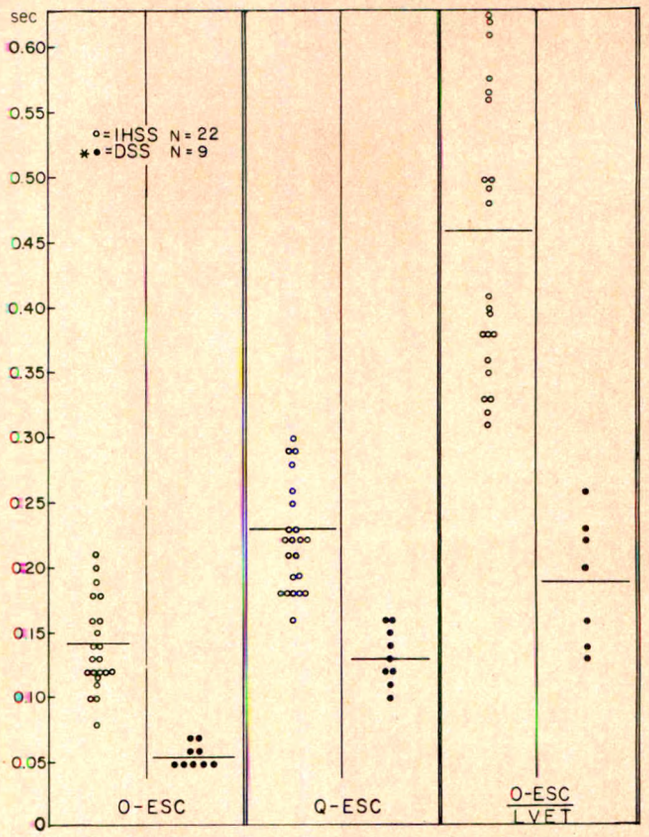


FIGURE 4. Preoperative comparison of aortic valve intervals in patients with discrete subaortic stenosis (DSS) and in patients with idiopathic hypertrophic subaortic stenosis (IHSS) and a resting intraventricular pressure gradient. There is a clear distinction between the two groups for all intervals. In the group with idiopathic hypertrophic subaortic stenosis, the intervals were 0.23 ± 0.04 second for Q-ESC, 0.14 ± 0.04 second for O-ESC, and 0.45 ± 0.11 for O-ESC/LVET (mean ± standard deviation). In the group with discrete subaortic stenosis, the respective values were 0.13 ± 0.02 second, 0.05 ± 0.01 second and 0.19 ± 0.05. The differences between the two groups were highly significant ($P < 0.01$). Mean values are indicated by **horizontal lines.** *O-ESC/LVET could be measured in only seven patients with discrete subaortic stenosis. N = number of patients; other abbreviations and definitions as in Figure 1.

Preoperatively, early systolic closure occurred in 22 patients with a resting intraventricular pressure gradient (Fig. 3A). Coarse fluttering was present in every patient. Postoperatively, results of echocardiography and cardiac catheterization were available for study in 12 patients (Table II). In 8 of the 12 the early systolic closure was no longer present and there was no resting gradient at the time of postoperative cardiac catheterization (Fig. 3B). Three patients with a residual gradient at rest of 22, 45 and 100 mm Hg, respectively, had persistent early systolic closure. One patient (Case 6, Table II) had a postoperative gradient of only 10 mm Hg and no early systolic closure. Fluttering persisted although it was attenuated in all patients who underwent operation.

Q-O, Q-ESC, O-ESC intervals and O-ESC/LVET: The difference between patients with discrete subaortic stenosis and idiopathic hypertrophic subaortic stenosis was significant ($P < 0.01$) for all measured intervals except Q-O (Fig. 4), which was the same for both groups (0.08 ± 0.02 second). The Q-ESC interval was 0.13 ± 0.02 second in patients with discrete subaortic stenosis and 0.23 ± 0.04 second in patients with idiopathic hypertrophic subaortic stenosis. O-ESC was 0.05 ± 0.01 second in the former group and 0.14 ± 0.04 second in the latter. O-ESC/LVET was 0.19 ± 0.05 in the former and 0.46 ± 0.10 in the latter.

Discussion

In patients with discrete subaortic stenosis the left ventricular outflow tract obstruction is caused by a fixed subaortic diaphragm, a fibromuscular collar or a tunnel-like narrowing.[23] In idiopathic hypertrophic subaortic stenosis, conversely, the stenosis is believed to be dynamic, provoked by the apposition of the anterior leaflet of the mitral valve to the thickened interven-

tricular septum in systole.[17] Previous investigators have reported that in both conditions early systolic closure and fluttering of the aortic valve can be recorded.[4–14]

Discrete subaortic stenosis: All nine patients with discrete subaortic stenosis had early systolic closure of one or both aortic cusps in the preoperative echocardiogram. Previous reports[11,12] have suggested that these abnormalities may disappear after operation, but in five of six patients in our study the early systolic closure persisted after operation. We could not determine whether this persistence was caused by an associated malformation of the aortic cusps or incomplete relief of the obstruction.[18,23] Only one patient (Case 2, Table I) underwent postoperative cardiac catheterization. This patient had no systolic gradient, and no early systolic closure of the aortic valve was seen in the echocardiogram. We were not able to identify the subaortic membrane or a part thereof by means of echocardiography. This was also the experience of others.[9]

The mechanism of early systolic closure of the aortic valve in patients with discrete subaortic stenosis is not clearly understood. Suggestions have been made that because of the fixed obstruction, a jet of turbulent blood alters normal motion of the aortic cusps.[9] Whether one or both cusps are affected probably depends upon the direction of the jet of blood.[10]

Idiopathic hypertrophic subaortic stenosis: Systolic anterior motion of the mitral valve has been used as a qualitative and quantitative indicator of the severity of the subaortic gradient in idiopathic hypertrophic subaortic stenosis.[15–17] It has been emphasized that both the anterior and posterior mitral leaflets must be simultaneously visualized in order to estimate the degree of obstruction.[17] However, various technical problems may hamper satisfactory visualization of the mitral valve.[24] Occasionally, only the extreme tip of the anterior mitral leaflet will show systolic anterior motion and thus the abnormality may be missed.[17] In addition, after mitral valve replacement or anuloplasty, systolic anterior motion of the mitral valve cannot be used to determine the presence or absence of a left ventricular outflow tract gradient. Because of these limitations, we attempted to determine if early systolic closure of the aortic valve might be helpful in supplementing the echocardiographic evaluation of idiopathic subaortic stenosis.

Early to mid systolic closure of the aortic valve has been described in patients with idiopathic hypertrophic subaortic stenosis but has not been investigated thoroughly.[5–8] An underlying abnormality of the dynamics of left ventricular ejection has been suggested as a cause for early to mid systolic closure.[6] As reported by Boughner et al.,[6] idiopathic hypertrophic subaortic stenosis is characterized by a sharp early peak in flow velocity followed by a rapid decrease in mid systole and a second slower peak in late systole. On echocardiography these findings correspond to the motion of the aortic cusps. The peak blood flow velocity occurred at the time of the maximal separation of the cusps, and the rapid decrease in velocity in mid systole occurred at the point of early systolic closure. Approximately 80 percent of the stroke volume is ejected during the first half of systole in patients with idiopathic hypertrophic subaortic stenosis according to various authors.[25–27]

In our patients with idiopathic hypertrophic subaortic stenosis, early systolic closure was a sensitive indicator of the resting intraventricular pressure gradient before operation. After operation, in every instance the early systolic closure disappeared with elimination of the resting gradient. One patient (Case 6, Table II) with a resting gradient of only 10 mm Hg also had normal motion of the aortic valve. These observations are in agreement with the experience of Boughner et al.,[6,7] who reported early systolic closure of the aortic valve in a patient with a gradient of 60 mm Hg but normal motion of the aortic valve in another patient with a gradient of 18 mm Hg at rest. Three of our patients who had a residual postoperative gradient of 22, 45 and 100 mm Hg, respectively, showed persistence of early systolic closure of the aortic valve. These findings indicate that early systolic closure of the aortic valve in idiopathic hypertrophic subaortic stenosis is a reliable indicator of a significant resting left ventricular outflow gradient, not only before but also after operation. Early systolic closure did not occur when there was a gradient of less than 20 mm Hg.

Correlation of early systolic change and degree of ventricular obstruction: To determine if the time of maximal early systolic closure is related to the degree of left ventricular outflow tract gradient, we compared the preoperative gradient and Q-ESC intervals in 22 patients with idiopathic hypertrophic subaortic stenosis. We found no significant correlation ($r = -0.28$) between the degree of obstruction and the time of early systolic closure.

The lability of the resting intraventricular obstruction in idiopathic hypertrophic subaortic stenosis is well known. It is theoretically possible that at the time of echocardiography a gradient could exist that was not recorded during cardiac catheterization and vice versa. Care was taken to perform both investigations without altering the resting basal conditions. The consistency of our results substantiates our contention; that is, no patient with a resting pressure gradient above 10 mm Hg failed to show early systolic closure of the aortic valve, and no patient without a resting pressure gradient showed early systolic closure of the aortic valve.

Differentiation of hypertrophic and discrete subaortic stenosis: In our study early systolic closure of the aortic valve occurred later in the patients with idiopathic hypertrophic subaortic stenosis than in those with discrete subaortic stenosis. All measured intervals except Q-O were clearly different in these two groups. We believe that the time of occurrence of early systolic closure is a reliable echocardiographic finding and can be used to distinguish between idiopathic hypertrophic and discrete subaortic stenosis.

We encountered only one patient with coexisting discrete and idiopathic hypertrophic subaortic stenosis (Case 3, Table I). Left ventricular angiography revealed a cone-shaped subvalve chamber as well as severe left ventricular hypertrophy and cavity obliteration in

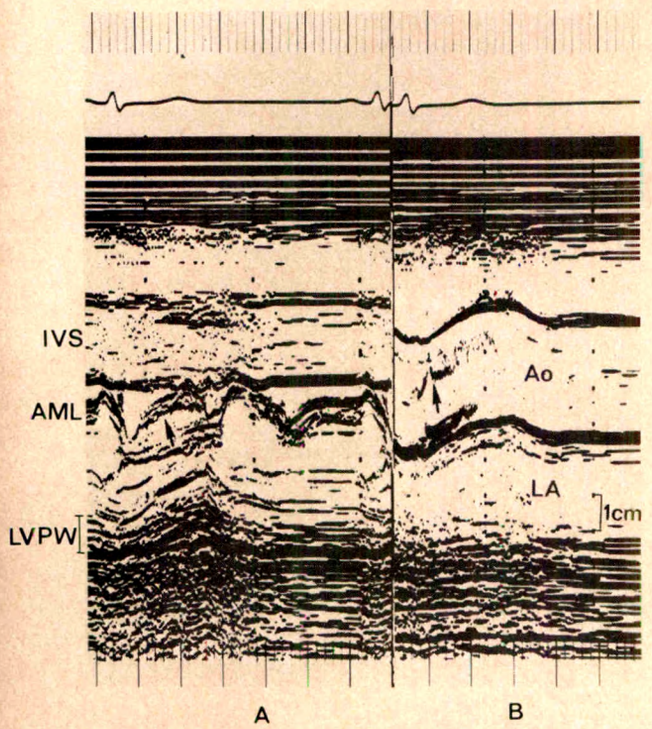


FIGURE 5. Case 3, Table I. Echocardiogram of a patient with discrete subaortic stenosis and coexisting idiopathic hypertrophic subaortic stenosis. **A,** note the asymmetric hypertrophy of the interventricular septum (IVS) in relation to the left ventricular posterior wall (LVPW), and the systolic anterior motion **(arrow)** of the anterior mitral leaflet (AML). **B,** the aortic valve shows early systolic closure occurring 0.05 second after opening **(arrow).** Ao = aorta; LA = left atrium.

systole. The peak systolic gradient across the left ventricular outflow tract was 85 mm Hg. Echocardiography disclosed asymmetric septal hypertrophy and systolic anterior motion of the mitral valve (Fig. 5), consistent with idiopathic hypertrophic subaortic stenosis. However, early systolic closure of the aortic valve was within the range of values for discrete subaortic stenosis (the O-ESC interval was 0.05 second). The presence of a subvalve membrane was confirmed at operation.

Krueger et al.[28] described a patient with combined membranous and hypertrophic subvalve aortic stenosis who also exhibited premature aortic valve closure beginning immediately after opening. The aortic valve motion in these two patients appears to suggest that the presence of discrete subaortic stenosis can be identified with echocardiography even when idiopathic hypertrophic subaortic stenosis coexists.

A possible explanation of the difference in timing of early systolic closure is that, in patients with discrete subaortic stenosis, such closure is caused by blood vortexes that are produced beyond the fixed orifice as soon as ejection occurs.[9] In idiopathic hypertrophic subaortic stenosis, however, aortic flow is unimpeded and actually faster than normal in the first part of systole but is decreased notably by mid systole.[25–27] Early systolic closure is recorded approximately at that point; therefore, we believe that it is related to the pattern of aortic flow.

Fine fluttering of the aortic leaflets: This sign can be recorded in normal persons.[29] High amplitude fluttering of the aortic cusps is present in both idiopathic hypertrophic and discrete subaortic stenosis and does not appear to be relieved by surgical treatment. In our experience the usefulness of this sign is limited. It is also possible that gross fluttering of the aortic cusps makes identification of the point of early systolic closure difficult, although this has not been true in our patients.

Implications: Although early systolic closure of the aortic valve appears to be a consistent finding in idiopathic hypertrophic subaortic stenosis with a resting gradient and in discrete subaortic stenosis, it has occasionally been seen in other disorders.[11,30] In these instances, additional echocardiographic and clinical information may be necessary to determine the appropriate diagnosis.

Echocardiographic analysis of the motion of the aortic valve is an important adjunct to already established echocardiographic measurements in the diagnosis and follow-up of patients with idiopathic hypertrophic and discrete subaortic stenosis.

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Determinants of the Amplitude of the Aortic Component of The Second Heart Sound in Aortic Stenosis

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The characteristics of the aortic component of the second heart sound in calcific and congenital noncalcific aortic stenosis were studied to determine a cause for observed differences. Intraarterial pressure and sound were measured above the aortic valve in 20 patients utilizing catheter-tip micromanometers. Ten patients had a normally functioning aortic valve, six had calcific aortic stenosis and four had congenital noncalcific aortic stenosis. As expected, the aortic sound was diminished in patients with calcific aortic stenosis compared with that in patients with a normal valve (600 ± 200 versus 2,600 ± 200 dynes/cm^2 ($P < 0.001$). In patients with congenital aortic stenosis, sound amplitude was not reduced compared with that in patients with a normal valve. Measurement of sound produced by closure of normal and stenotic valves in an in vitro model of the circulatory system yielded comparable results. In vitro high speed (2,000 frames/sec) motion pictures of the diastolic motion of the closed cusps showed vibrations of comparable magnitude in the normal porcine and the simulated congenitally stenotic valve. The calcified stenotic valve showed no noticeable diastolic vibrations. These observations indicate an association between the amplitude of the second heart sound and diastolic vibrations of the closed cusps. A calcified stenotic valve, being thick and stiff, would have a diminished ability to vibrate and would therefore produce a diminished sound. A congenitally stenotic valve, in contradistinction, if not yet damaged by degenerative changes, would not be limited in its ability to vibrate during diastole and would therefore produce a normal second sound.

A diminished or absent aortic component of the second heart sound is known to occur in acquired aortic stenosis.[1–5] The paradoxical presence of a normal aortic component of the second sound in young patients with congenital membranous noncalcific aortic stenosis is also recognized.[6,7] Investigators have suggested several possible, but somewhat contradictory, mechanisms of the reduced amplitude of the second heart sound in patients with acquired calcific aortic stenosis.[2,5] Some[5] have suggested that the amplitude would be reduced if the aortic valve were largely approximated before retrograde flow is well established. Others[2] have suggested that the delayed rebound of aortic flow caused by delayed closure of the aortic valve, decreased filling and poststenotic dilatation, may be responsible. The difference in sound amplitude in calcific and congenital noncalcific aortic stenosis is not explained by either mechanism, but immobility of the cusps is thought to play a role.[8] In this study we explored the pathophysiologic circumstances that would produce a diminished second sound in acquired calcific aortic stenosis and permit its continued presence in congenital aortic stenosis.

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TABLE I

Age, Hemodynamic Measurements and Aortic Sound Amplitude in 20 Patients

Case Number	Age (yr)	HR	Ao Press (mm Hg)	CO	Valve Area (cm^2)	Systolic Pressure Gradient (mm Hg)	Amplitude of Aortic Sound (dynes/cm^2)	AI
Patients With a Normal Aortic Valve								
1	67	90	169/84	...	...	2700	0	0
2	43	82	120/62	5.0	...	2200	0	0
3	38	84	90/58	6.8	...	2400	0	0
4	53	78	128/82	5.4	...	2100	0	0
5	30	90	136/80	...	...	2000	0	0
6	44	96	120/78	7.5	...	1900	0	0
7	40	60	110/72	5.3	...	3800	0	0
8	51	90	100/60	5.2	...	2800	0	0
9	48	66	130/80	4.1	...	2200	0	0
10	50	84	120/80	6.4	...	3400	0	0
Mean	46	82	122/74	5.7	...	2600	...	...
±SEM	±3	±4	±7/3	±0.4	...	±200	...	...
Patients With Calcific Aortic Stenosis								
11	48	80	122/70	4.4	0.52	68	500	0
12	62	70	154/76	5.4	1.00	52	500	1+
13	65	54	120/60	4.5	0.41	108	600	1+
14	34	78	116/68	4.6	0.42	124	1200	1+
15	67	52	90/50	3.3	0.39	85	100	0
16	67	84	128/62	2.5	0.18	112	900	2+
Mean	57	70	122/64	4.1	0.49	92	600	...
± SEM	±5	±6	±8/3	±0.4	±0.11	±11	±200	...
Patients With Congenital Noncalcific Aortic Stenosis								
17	35	60	102/60	5.6	...	12	3000	0
18	20	126	96/74	4.0	0.27	72	6500	0
19	13	84	118/87	...	0.80	96	2200	0
20	20	80	82/58	6.6	1.50	32	2700	0
Mean	22	88	99/70	5.0	0.86	53	3600	...
±SEM	±5	±14	±7/7	±0.8	±0.36	±19	±1000	...

AI = aortic insufficiency; Ao Press = aortic pressure (mm Hg); CO = cardiac output (liters/min); HR = heart rate (beats/min); SEM = standard error of the mean.

Methods

Patients: Twenty patients were studied during diagnostic cardiac catheterization. Ten patients (five with angina pectoris and normal vessels, four with coronary artery disease and one with pericarditis) had a normal aortic valve as judged from the absence of both a pressure gradient across the valve and either a systolic or a diastolic murmur. Six patients had calcific aortic stenosis as judged from the presence of a pressure gradient across the valve and the visualization of calcium on image intensification fluoroscopy. The calculated valve area of these patients ranged between 0.18 and 1.00 cm^2 (Table I). The peak pressure gradient across the valve ranged between 52 and 124 mm Hg. No patient had more than 2+ aortic insufficiency[9] (Table I), as defined by incomplete clearance of dye after the first systole without progressive opacification of the ventricle. Four patients had congenital membranous aortic stenosis. None showed calcium in the region of the valve, and none had aortic insufficiency. A bicuspid valve was found at operation in one of the four patients, and two manifested a bicuspid valve on orifice view aortography.[10] The pressure gradient across the valve of these four patients ranged between 12 and 96 mm Hg (Table I).

Intraaortic sound measurements: Pressure and sound pressure (referred to as intraaortic sound) were measured above the aortic valve in all patients with use of a catheter-tip micromanometer (Millar Instruments, Inc., Houston, Texas). The tip of the catheter was advanced until contact with the aortic cusps was made and was then withdrawn 1 or 2 cm from the valve to achieve a uniform position near the valve in all patients. The frequency response of the catheter-tip micromanometer was 0 to 10 kilohertz. Both intracardiac pressure and sound were measured through the same transducer by filtering the low frequency components of the pressure signal and amplifying the upper frequency range. The low frequency cut-off in the sound mode, when used with 10 megohm loading, was 6 decibels at 40 hertz, 3 decibels at 50 hertz and flat above 90 hertz.

The peak sound pressure for any specified time interval is the maximal absolute value of the instantaneous pressure in that interval expressed in dynes/cm^2.[11] We therefore calibrated intracardiac sound in these units. The sound mode with the system used amplifies sound pressure 11 times greater than pressure signals. This amplification of the sound pressure relative to the pressure was determined by the manufacturer. To obtain a calibration of sound, we attached the output of the pressure mode to the sound amplifier and inserted an electrical signal that was equivalent to 20 mm Hg on the pressure mode. This same signal would therefore be equal to 1.82 mm Hg if it were recorded directly from the sound mode. Recordings of pressure and sound were obtained on an Electronics for Medicine VR-6 photographic recorder at speeds of 25 to 200 mm/sec. The frequency response of the recording system was flat to 700 hertz with a 3 decibel decrease at 2,100 hertz. Sound and pressure recordings were filtered at 250 hertz. When sound and pressure were filtered at 2,500 hertz, no noticeable difference of amplitude of sound and pressure was noted.

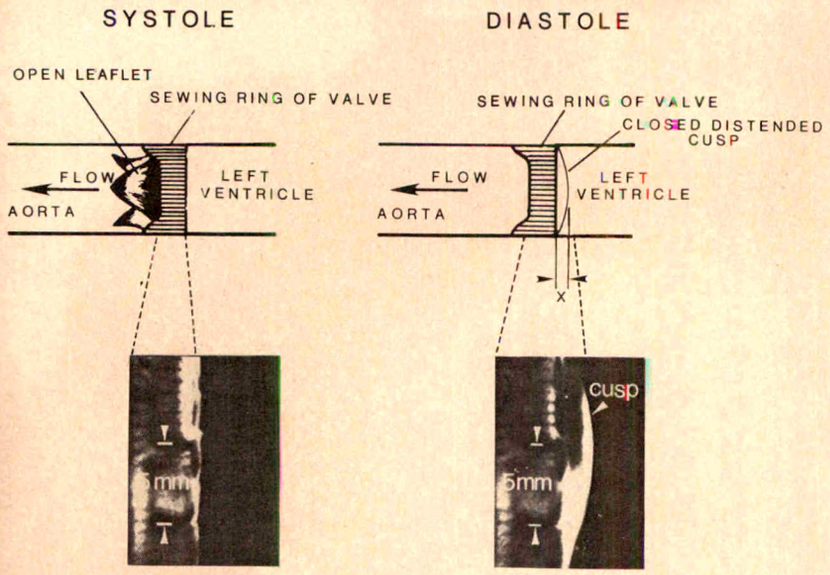


FIGURE 1. Above, diagrams of mounted valve in the hydraulic model of the cardiovascular system used in this study. During systole **(left),** the cusps are not visible on the ventricular side of the mounting ring of the valve. During diastole **(right),** the cusps bulge toward the simulated ventricle. The magnitude of deflection was measured on each frame of the motion picture as the distance x. **Below,** enlarged frames of high speed cinefilm show the sewing ring and distended cusp during diastole.

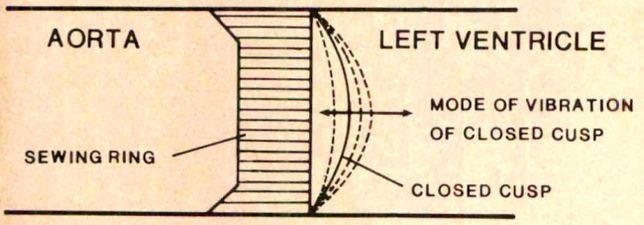


FIGURE 2. Diagram (not to scale) of mounted normal porcine valve showing diastolic vibration of a closed aortic cusp.

Studies in vitro: Studies of the diastolic leaflet motion of a stented normal porcine valve (Hancock Laboratories Inc., Anaheim, California), a calcified stenotic human valve and a porcine simulated congenitally stenotic valve were conducted in vitro utilizing a Plexiglas® model of the root of the aorta and ventricular outflow tract. The circulating system utilized has been described in detail.[12,13] The calcified stenotic valve was obtained intact at operation and was subsequently mounted on a stent. The simulated congenitally stenotic valve was constructed by suturing together the leaflets of a normal porcine valve leaving a small central opening. None of the valves were regurgitant.

The diastolic vibrations of the closed cusps of each valve were photographed at 90° to the direction of flow, which allowed the viewer to note the motion of one cusp relative to the fixed stent (Fig. 1 and 2). All cinefilms of leaflet motion were taken at 2,000 frames/sec utilizing a high speed camera (Hycam, Red Lake Laboratories, Santa Clara, California). Pressure and sound above each of the valves were measured during the filming of valve motion by utilization of a catheter-tip micromanometer inserted just distal to the valve through an orifice in the Plexiglas model. The position of the tip of the catheter was maintained at a constant distance for all three valves. The gain of the sound amplifier was also maintained at a constant level to assure a proper comparison of the amplitude of the closure sound of the various valves. Sound and pressure were recorded on a VR-6 recorder as described in patients. Studies of each of the valves were performed with a simulated aortic pressure of 140/80 mm Hg, a pump rate of 70 strokes/min and a stroke volume of 70 ml/stroke. The systolic ejection period in each case was 0.3 second.

Analysis of the diastolic deflections of the closed cusps was made from projections of each frame of the motion picture with use of a stop frame analytical projector. The deflection of the leaflet into the simulated ventricular outflow tract was measured from the edge of the stent to the margin of the cusp along the centerline of the leaflet (Fig. 1). Measurements were obtained on each frame of the cine film throughout diastole.

Results

In vivo measurements: The amplitude of the aortic component of the second heart sound was significantly smaller in patients with calcific aortic stenosis (600 ± 200 dynes/cm^2) than in normal subjects (2,600 ± 200 dynes/cm^2) (P <0.001) (Fig. 3 and 4; Table I). However, there was no significant difference between the amplitude of the second sound of patients with congenital noncalcific aortic stenosis (3,600 ± 1,000 dynes/cm^2) and that of patients with a normal aortic valve (Fig. 3 and 4; Table I).

There was no significant difference between the aortic pressure of patients with a normal aortic valve (122/74 ± 7/3 mm Hg) and that of patients with congenital aortic stenosis (99/70 ± 7/7 mm Hg). There was also no significant difference between the aortic pressure of patients with a normal aortic valve and patients with calcific aortic stenosis (122/64 ± 8/3 mm Hg).

The aortic valves excised at the time of valve replacement from the patients with calcific aortic stenosis showed thickened, fibrotic, nonpliable and stiffened cusps. The aortic valve excised at operation from one of the four patients with congenital aortic stenosis was bicuspid; both cusps were pliable and only slightly

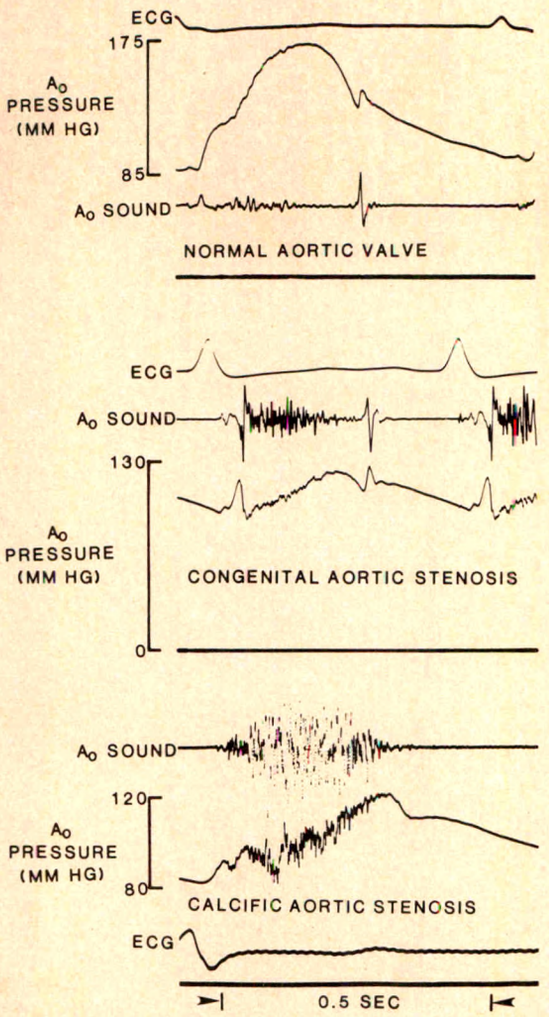


FIGURE 3. Aortic (A_0) pressure and sound tracings and electrocardiogram (ECG) in a patient with a normal aortic valve (Case 1) **(top),** a patient with congenital aortic stenosis (Case 12) **(center)** and a patient with calcific aortic stenosis (Case 20) **(bottom).** The amplitude of the aortic component of the second heart sound in the three patients was, respectively, 2,700, 6,500 and 1,200 dynes/cm^2.

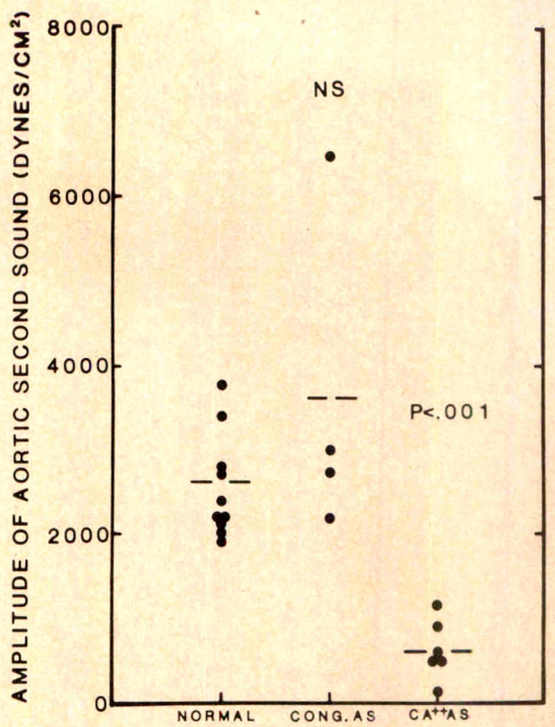


FIGURE 4. Amplitude of the aortic closure sound in patients with a normal aortic valve, congenital aortic stenosis (Cong. AS) and calcific aortic stenosis ($Ca^{++}AS$). In the latter group, sound amplitude was significantly less than in patients with a normal valve. Sound amplitude of patients with congenital aortic stenosis did not differ from that in patients with a normal valve. NS = not significant; P = probability.

thickened. The other two patients did not undergo valve replacement.

In vitro measurements of three types of valves: As in patients, the amplitude of the aortic sound was diminished in calcific aortic stenosis; however, it remained normal with a simulated congenitally stenotic valve (Fig. 5).

High speed motion pictures, in vitro, of the diastolic motion of the closed aortic cusps showed diastolic vibrations of the cusps of both the normal porcine and the simulated congenitally stenotic valves. However, no diastolic vibrations of the closed cusps of the calcified stenotic valve could be detected (Fig. 5 and 6). A high amplitude sound accompanied the valve vibrations of the normal porcine and simulated congenitally stenotic valve. Sound was markedly diminished when diastolic valve vibrations were too small to be visualized (Fig. 5 and 6).

Discussion

Second sound in calcific versus noncalcific aortic stenosis: Valve leaflets that are pliable, thin and stretchable and therefore capable of vibrating after closure were shown to produce a second sound of normal intensity. Such leaflets are present in normal valves or in valves that are congenitally stenotic and not yet damaged by degenerative changes. Valve leaflets that are rigid, thickened and not stretchable and therefore limited in ability to vibrate after closure were shown to produce a diminished second sound. Such leaflets are found in calcific aortic stenosis. These observations are in accordance with the concept that the second heart sound is produced by diastolic vibration of the closed cusps.[12,14] The aortic valve, as it vibrates during early diastole, causes compression and rarefaction of the blood within the ventricle and aorta that result in the generation of sound.[12] In this regard, the action of a closed semilunar valve is analogous to that of a vibrating membrane.[12,14] With this mechanism, it is possible to explain the paradoxical difference of behavior of the second heart sound in calcific and congenital noncalcific aortic stenosis on the basis of ability of the valve to vibrate after closure.

The motion of the semilunar valves in early diastole has been thought by several investigators[2,15–19] to be a

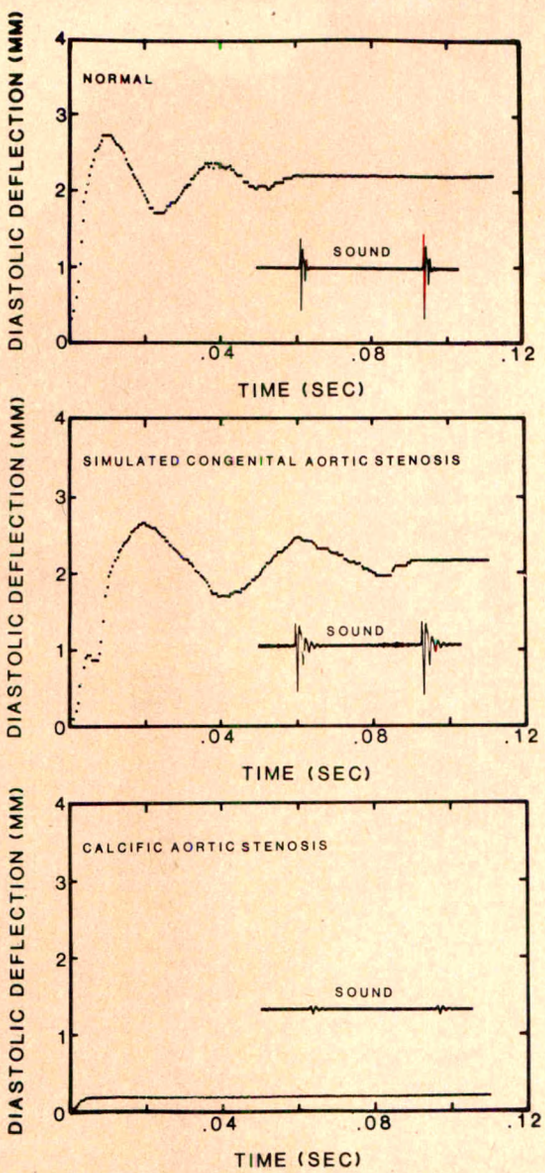


FIGURE 5. Diastolic motion of the normal porcine valve **(top),** simulated congenitally stenotic valve **(center)** and human calcified stenotic valve **(bottom).** Deflection toward the simulated ventricle is shown in millimeters and was measured as the distance x in Figure 1. The closure sound produced by each of these valves was recorded during the motion pictures and is shown with the vibrations. The gain of the sound was the same in each instance.

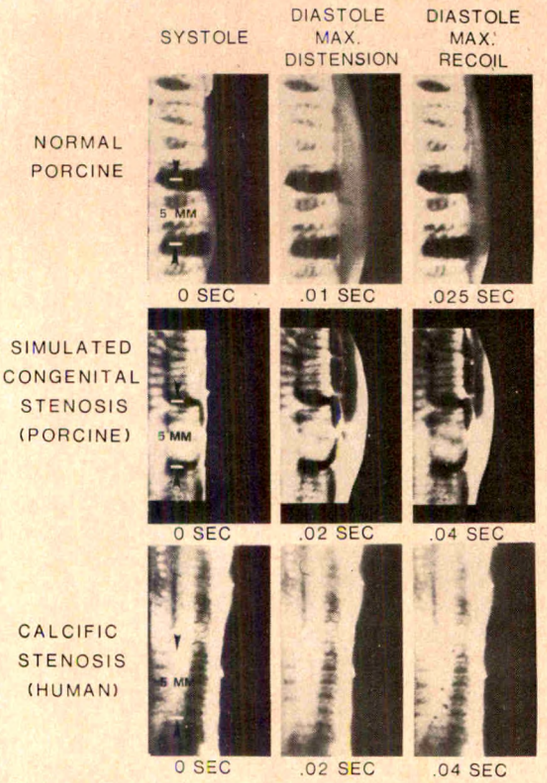


FIGURE 6. Selected frames from the high speed motion pictures of the mounted normal porcine valve **(top),** a simulated congenitally stenotic porcine valve **(center)** and a calcified stenotic human valve **(bottom).** The valve is oriented as shown in Figures 1 and 2. The sewing ring of the valve (extending vertically) is shown to the left of each frame and a 5 mm scale has been superimposed on the sewing ring. The ventricular side of the valve is to the right of each frame. Consequently, during the last portion of systole (time 0) the leaflets, being open, are not visible on the ventricular side of the sewing ring. During diastole, the leaflets after closure stretch toward the ventricles. Maximal (MAX.) stretch toward the ventricle during diastole is shown in the **middle frame, top row,** for the normal porcine valve and in the **middle frame, center row,** for the valve with simulated congenital stenosis. The frame at **top right** shows recoil of the distended aortic cusps toward the aorta and the frame at **right center** shows recoil of the simulated congenitally stenotic valve. The **bottom frames** of a human calcific stenotic valve show no distension of the closed cusp at any time after closure.

major factor in the origin of the second heart sound. Investigations in our laboratory[12,20] confirm the validity of this hypothesis and indicate that valve vibrations immediately after closure are of primary importance in the origin of both the second sound and the incisura of the central aortic pressure.

Other factors affecting amplitude of second sound: A regurgitant aortic valve is also associated with a reduced second heart sound.[21] Presumably diastolic vibration of an insufficient valve is impaired. Aortic regurgitation, if it accompanies aortic stenosis, would contribute to the diminished second sound. In our study, 19 of the 20 patients had 0 to 1+ aortic insufficiency; 1 had 2+ aortic insufficiency.[9]

Other factors may also contribute to the changes in sound amplitude that we observed. A relation between the rate of change of the diastolic pressure gradient and the amplitude of the aortic component of the second sound was shown in dogs[22,23] and in patients with a normal aortic valve.[24] We[23–25] previously showed that the rate of change of the diastolic pressure gradient is directly related to the rate of isovolumic relaxation. The rate of development of the pressure difference between the aorta and the ventricle during diastole possibly may vary in aortic stenosis, and this variation could contribute to alterations of the amplitude of the second sound. Perhaps a high rate of change of the diastolic

pressure gradient contributed to the large amplitude of the second sound in Patient 2 with congenital aortic stenosis.

Additional variables, not yet explored, are likely to affect the amplitude of the second heart sound.[26] These include the cross-sectional area of the valve, the volume and shape of the ventricle and the sound absorption coefficient of the walls of the ventricle. These factors may change in aortic stenosis and perhaps participate in affecting the amplitude of the second sound. It seems likely, however, that increased stiffness of the aortic valve is the predominant cause of the diminished sound in calcific aortic stenosis.

Oakley and Hallidie-Smith[8] suggested that the reduced amplitude of the second heart sound in patients with calcific aortic stenosis was due to the immobility of such calcified valves. They indicated that the normal amplitude of the second sound in congenital aortic stenosis resulted from continued mobility of the congenitally stenotic valve. We believe that mobility of the valve relates to the amplitude of the second sound only in a special sense. It is the diastolic vibration of the valve that produces the second sound.[12] Specifically, it is the capability of the valve to distend and recoil during early diastole that is retained in congenital aortic stenosis and lost in calcific stenosis. Only in this special sense does mobility of the valve relate to the intensity of the second sound.

In conclusion, pathologic processes that stiffen the leaflets in the course of producing stenosis, as in calcific aortic stenosis, would diminish the aortic component of the second heart sound by diminishing the capability of the valve to vibrate after closure. When the leaflets are pliable, as in patients with a normal valve or a congenitally stenotic valve that has not yet undergone degenerative changes, the second sound would be of normal amplitude because the ability of the valve to vibrate during diastole is not affected.

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Assessment of Mitral Valve E Point-Septal Separation as an Index of Left Ventricular Performance in Patients With Acute and Previous Myocardial Infarction

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A new echocardiographic index of left ventricular function, mitral valve E point-septal separation, was compared with the radionuclide ejection fraction determined using the first pass method in 60 patients (73 studies) with ischemic heart disease. Thirty-eight patients had acute myocardial infarction and 22 patients were studied an average of 24 months after acute infarction. In 30 normal subjects, E point-septal separation ranged from 0 to 5.4 mm (average 1.3 mm). In 57 studies (78 percent) E point-septal separation correctly identified patients with a normal or reduced ejection fraction (less than 0.52), but in 13 studies (18 percent) E point-septal separation was normal and ejection fraction depressed. In only three studies (4 percent) was there a normal ejection fraction and an abnormal E point-septal separation. Results did not differ between patients with acute infarction and those studied late after infarction. An E point-septal separation of more than 5.5 mm was highly specific (92 percent) for a reduced ejection fraction, but the sensitivity rate was only 65 percent. Abnormal wall motion as assessed with echocardiography or video-tracking, or both, occurred equally among patients with normal and increased E point-septal separation, but this measure was less accurate in patients with more severe wall motion abnormalities. E point-septal separation was unrelated to heart rate; an abnormal value was equally distributed among patients with a normal and those with an enlarged left ventricular end-diastolic dimension on echocardiography. E point-septal separation was superior to other echocardiographic indexes of left ventricular function (percent of fractional shortening, mean rate of diameter shortening and ejection fraction). Thus, E point-septal separation is a simple noninvasive measure of left ventricular function. We conclude that an abnormal E point-septal separation is useful for identifying depressed left ventricular function in patients with acute myocardial infarction and chronic ischemic heart disease. However, 28 percent of our patients with a normal E point-septal separation had a depressed radionuclide ejection fraction. Therefore a normal value for E point-septal separation does not exclude the presence of abnormal left ventricular function in such patients.

Massie et al.[1] have proposed that measurement of the separation of the E point of the mitral valve echogram from the interventricular septum can be employed as an index of left ventricular function. These investigators noted that the E point of the anterior leaflet of the mitral valve approximates the interventricular septum in normal subjects. Measuring the minimal E point-septal separation from several echographic views, they reported that this distance did not exceed 4 mm in normal subjects or 5 mm in patients with coronary artery disease. Patients with a normal ejection fraction as measured from biplane angiography also exhibited minimal E point-septal separation, whereas an increased E point-septal separation was found in patients with a reduced ejection fraction. Al-

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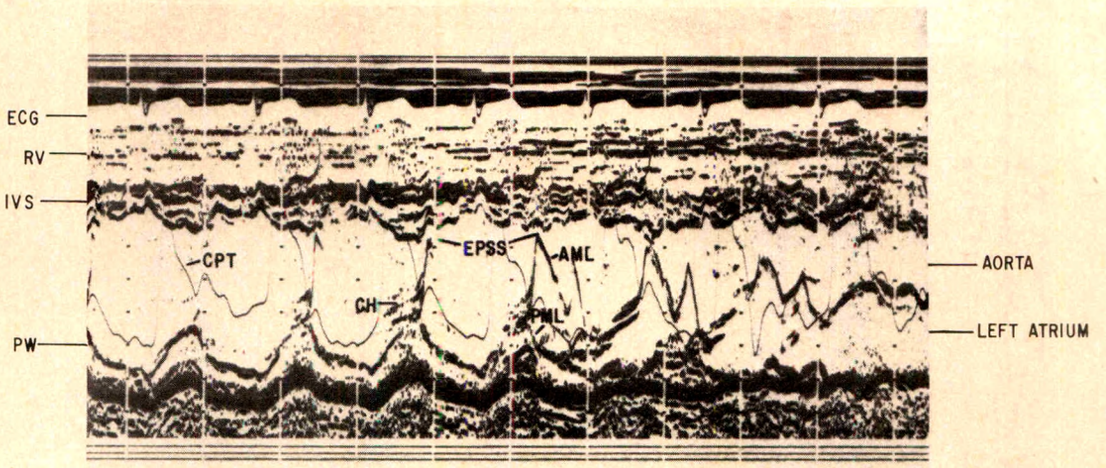


FIGURE 1. A normal sweep from the left ventricular cavity to the aorta and left atrium is shown. Just beyond the junction of the left atrium and the left ventricular cavity, anterior mitral leaflet (AML) motion is combined with motion of the posterior aortic wall. The septum moves anteriorly in this transition area where the anterior aortic wall becomes continuous with the interventricular septum (IVS). Further into the left ventricular cavity the full mitral valve, with anterior and posterior leaflets (PML) visible, is seen. The septum is near the "hinge point" and its motion is reduced. Still lower in the chamber normal septal and left ventricular posterior wall (PW) motion are apparent. As indicated in the text, septal motion and left ventricular measurements were obtained in an echocardiographic view even farther down in the left ventricular cavity where posterior chordae (CH) and portions of the anterior mitral valve leaflet are recorded, as shown in the first three beats on the left. In all cases, the minimal E point-septal separation could be obtained by measurement in a view where the full mitral valve (anterior and posterior leaflets) are displayed, as shown here. The establishment of this criterion for measuring E point-septal separation insured consistency of measurement location among different patients. CPT = carotid arterial pulse tracing; ECG = electrocardiogram; EPSS = E point-septal separation; RV = right ventricular cavity.

though they documented a strong negative correlation between E point-septal separation and ejection fraction, no patients with acute myocardial infarction were studied. Because echocardiographic evaluation of left ventricular funciion may not be reliable in patients with coronary artery disease,[2] we undertook this study to evaluate the use of E point-septal separation as an index of left ventricular function in patients with acute myocardial infarction as well as in patients with chronic ischemic heart disease who also had a previously documented myocardial infarction.

Subjects

Sixty patients with well documented myocardial infarction were studied using echocardiography, wall motion videotracking[3] and radionuclide angiocardiography.[4] Of the 60 patients, 48 were men aged 32 to 80 years (mean 56.5), and 12 were women aged 59 to 77 years (mean 68.3). Ten patients were studied on more than one occasion, bringing the total number of studies to 73. Thirty-eight patients had acute myocardial infarction; the remaining 22 were studied an average of 24 months after acute infarction. In the patients with acute infarction, all studies were completed an average of 3 days after infarction (range 0 to 6 days, except for three patients who were studied 9, 15 and 17 days, respectively, after acute infarction). No patient had evidence on physical examination or echocardiogram of either aortic regurgitation or mitral stenosis.[1] In addition, 30 normal volunteers were studied with echocardiography alone. This group included 20 men aged 24 to 34 years (mean 27.0) and 10 women aged 21 to 27 years (mean 24.4). None of the 30 volunteers had any evidence of cardiac disease on history, physical examination, electrocardiogram or echocardiography.

Echocardiography, wall motion videotracking and radionuclide angiocardiography were all performed within 4 hours of each other in 49 of the 73 studies (67 percent). In 23 studies the three procedures were performed within 24 hours; in the remaining instance the three procedures were done within 4 days of each other. None of the patients had any significant change in their condition during the time required to complete the three studies, as judged from alterations in heart rate, blood pressure, electrocardiograms or general physical examination. All patients had sinus rhythm at the time of study.

The diagnosis of myocardial infarction was based on at least two of the following criteria: (1) a history of typical prolonged chest pain; (2) acute electrocardiographic changes of myocardial injury with evolution of a characteristic infarct pattern; (3) serial serum enzyme (creatine kinase [CK], glutamic oxaloacaetic transaminase [GOT] or lactic dehydrogenase [LDH]) elevations, alone or in combination.

Methods

Echocardiograms: These were obtained with a commercially available ultrasonoscope, the Picker Echoview II with a Honeywell Visicorder Oscillograph model 1856 for display and recording. A 2.25 megahertz, 1.25 cm transducer focused at 7.5 cm and a 1.6 megahertz, 1.9 cm transducer focused at 10 cm were used. Both transducers had repetition rates of 1,000 impulses/sec. Standard transducer placement techniques were used to visualize the left ventricle, mitral valve, interventricular septum, aorta and left atrium (Fig. 1). Simultaneous recordings of the carotid arterial pulse tracing and the lead II electrocardiogram were included in the echocardiogram.

Measurements of echocardiographic left ventricular dimensions were made to the nearest 0.5 mm, and the results

of all dimensional and functional measurements are expressed as the average of at least three beats. The beats used for these measurements had well defined septal and posterior wall endocardial surfaces. For dimensional and functional measurements, portions of the mitral valve and posterior chordal echoes were included to insure consistent localization of the ultrasonic beam as previously described[5–7] (Fig. 1). Left ventricular ejection time was measured between the rapid upstroke and the dicrotic notch of the carotid arterial pulse tracing. Left ventricular end-diastolic dimension was measured as the distance between endocardial surfaces of the septum and posterior wall coincident with the R wave of the electrocardiogram. Left ventricular end-systolic dimension was measured as the smallest distance between the posterior wall endocardium and a line drawn tangent to the most posterior systolic position reached by the septum. Septal motion was measured as the distance between the septal position at a time coincident with the R wave of the electrocardiogram to the most posterior systolic septal motion. Normal septal excursion in our laboratory ranges between 4 and 8 mm. Hypokinesia was defined as an excursion of less than 4 mm, akinesia as absence of excursion and hyperkinesia as excursion greater than 8 mm. Dyskinesia was defined as predominant anterior motion of the septum that occurred either early or late in systole.

These dimensional measurements were used to calculate end-diastolic volume and end-systolic volume by the method of Pombo and associates.[8] The percent internal diameter shortening, mean velocity of diameter shortening (Vcf) and ejection fraction were also obtained from these measurements.[5–7]

E point-septal separation was measured as the minimal distance between the E point of the anterior mitral valve leaflet to a line drawn tangent to the most posterior excursion of the interventricular septum within the same cardiac cycle. The E point of the anterior mitral valve leaflet was taken as the most anterior motion of this structure during diastole (Fig. 1). All beats in which the mitral valve and septum were clearly defined were examined. The view with the minimal E point-septal separation was used for measurement (Fig. 1). To assess the reproducibility of the method, measurements of E point-septal separation were performed in 20 persons (10 normal subjects and 10 patients) several hours to 4 months apart. The mean difference of this measurement was 1.0 mm (range 0 to 3.1). In no instance was the separation of normal from depressed left ventricular function altered by the repeat measurement. Interobserver variation in these 20 recordings (two observers) did not exceed 1 mm.

Wall motion videotracking: This procedure was performed with a commercially available instrument (Biotronix Heart Motion Videotracker).[3] The fluoroscopic cardiac image was displayed on a Plumbicon television system using a 23 cm image intensifier. The analog signal was either tracked directly or recorded on a Honeywell Visicorder photographic system for later analysis. The left ventricular silhouette was recorded in the 10° right anterior oblique, frontal, 15° left anterior oblique and lateral projections at five sites between the high and apical portions. A modification of Herman and Gorlin's terminology[9] was used to define left ventricular wall motion abnormalities. Dyskinesia was defined as a holosystolic paradoxical movement. Asynchrony was used to describe an early systolic bulge followed by inward motion or normal inward motion followed by a late systolic bulge. Akinesia was defined as a localized absence of wall motion. Hypokinesia described localized wall motion that was less than 50 percent of the motion of normal wall segments. Abnormal wall motion was defined by the presence of any of these abnormalities in any projection.

Radionuclide left ventricular ejection fraction: This measurement was obtained using the first pass radionuclide technique as described previously.[4] In brief, a bolus dose of technetium-99m pertechnetate (10 to 14 mCi contained in a volume of less than 1 ml 0.9 percent sodium chloride) was injected into a large median antecubital or external jugular vein. During the initial pass of the bolus dose through the heart, precordial activity was recorded with a gamma scintillation camera (Searle Pho-Gamma HP) equipped with a low energy high resolution parallel hole collimator in the 30° right anterior oblique position and stored in an event by event mode in a digital computer (Med II, General Electric Company). A region of interest was assigned to the left ventricular cavity and a high frequency left ventricular time-activity curve was generated. This curve was corrected for activity arising from noncardiac background structures. The resultant left ventricular time-activity curve is characterized by peaks and valleys corresponding to the left ventricular volume at end-diastole and end-systole, respectively. The difference in counts between end-diastole and end-systole represents the stroke volume, and division by the counts at end-diastole provides the ejection fraction. Left ventricular ejection fraction is calculated without assumptions regarding left ventricular geometry.[4] Previously, an excellent correlation has been reported between the ejection fraction derived with this radionuclide technique and the ejection fraction measured with biplane angiocardiography.[4]

Correlative criteria for E point-septal separation: *The following calculations were also made for E point-septal separation using the criteria for an abnormal value of 5.5 mm or more:*

1. *Specificity* = number of patients with normal E point-septal separation and a normal radionuclide ejection fraction (true negatives) divided by all patients with a normal radionuclide ejection fraction (true negatives and false positives).
2. *Sensitivity* = the number of patients with abnormal E point-septal separation and a reduced radionuclide ejection fraction (true positives) divided by all patients with reduced radionuclide ejection fraction (false negatives and true positives).
3. *Predictive value of an abnormal response* = the number of patients with abnormal E point-septal separation and a reduced radionuclide ejection fraction (true positives) divided by all patients with abnormal E point-septal separation (true positives and false positives).

The influence of heart rate on the E point-septal separation measurement was examined with the use of partial correlation coefficient analysis.[10] The correlation coefficient of E point-septal separation versus the radionuclide ejection fraction (r_{12}) was compared with the correlation coefficient of E point-septal separation versus the radionuclide ejection fraction when the influence of heart rate was kept constant ($R_{12.3}$). This type of approach permits regression analysis of two variables (E point-septal separation [subscript 1] versus radionuclide ejection fraction [subscript 2] when the effect of heart rate [subscript 3] is statistically removed; hence the notation $R_{12.3}$ in the following equation:

$$R_{12.3} = \frac{r_{12} - (r_{13})(r_{23})}{\sqrt{1 - (r_{13})^2}\sqrt{1 - (r_{23})^2}}$$

where r_{13} = the correlation coefficient for E point-septal separation versus heart rate; r_{23} = the correlation coefficient for radionuclide ejection fraction versus heart rate; r_{12} = the

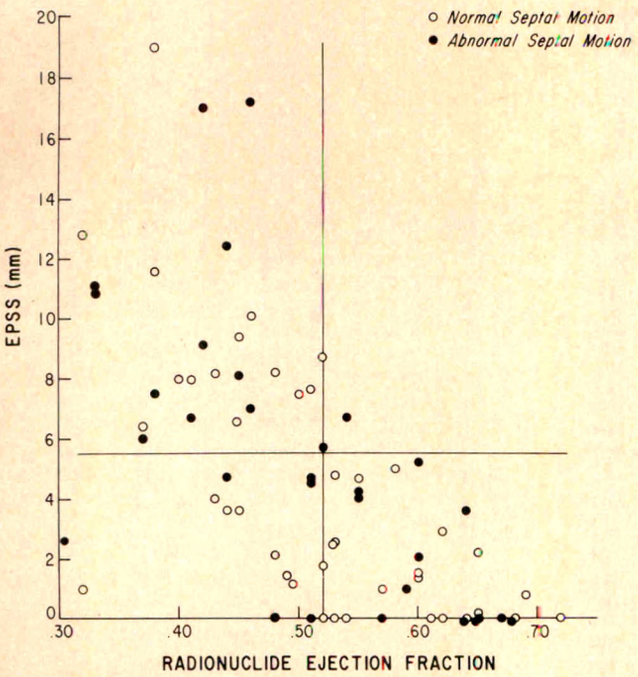


FIGURE 2. The relation between radionuclide ejection fraction and E point-septal separation (EPSS) is plotted for all studies. The **crossed lines** represent the lower limit of normal for radionuclide ejection fraction and the upper limits of normal for E point-septal separation. Abnormal septal motion in the echocardiogram appears to be equally distributed among patients with normal and increased E point-septal separation. For specificity and sensitivity of the method, see text.

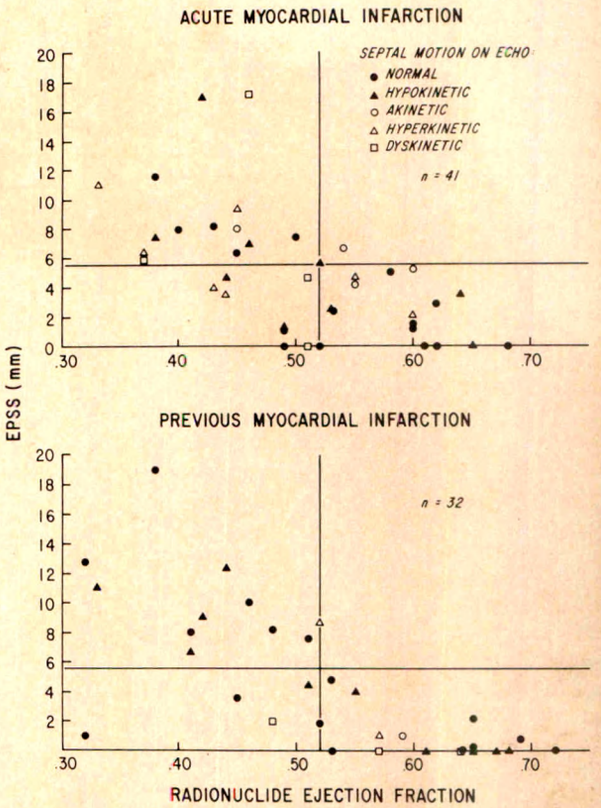


FIGURE 3. The relation between radionuclide ejection fraction and E point-septal separation (EPSS) is plotted separately for patients with acute (**upper panel**) and previous (**lower panel**) myocardial infarction. The **crossed lines** represent the lower limits of normal for the radionuclide ejection fraction and the upper limits of normal for E point-septal separation. Abnormalities in septal motion in the echocardiogram (ECHO) are defined by the symbols and appear to be equally distributed among patients with normal and increased E point-septal separation (see text). n = number of patients.

correlation coefficient for E point-septal separation versus radionuclide ejection fraction; and $r_{12.3}$ = the correlation coefficient for E point-septal separation versus radionuclide ejection fraction when the influence of the heart rate was held constant.

Results

E point-septal separation in normal subjects and in patients with ischemic heart disease: In 30 normal volunteers, E point-septal separation ranged from 0 to 5.4 mm (mean 1.3). Fifteen normal subjects (50 percent) had an E point-septal separation of 0 mm. Thus, an abnormal E point-septal separation was defined as greater than or equal to 5.5 mm. The results of the 73 patient studies are shown in Figure 2, where E point-septal separation is plotted against the radionuclide ejection fraction. There was a general inverse correlation between the two measures. Analysis reveals that 33 studies were true negatives; that is, there was a normal E point-septal separation and normal radionuclide ejection fraction (greater than 0.52). In 24 studies the E point-septal separation was abnormal (greater than 5.5 mm) and the ejection fraction was reduced (true positives). Thus, in 57 studies (78 percent) E point-septal separation correctly identified patients with a normal or reduced ejection fraction. By contrast, in 13 studies there was a normal E point-septal separation and a reduced radionuclide ejection fraction (false negatives) and in only three studies was the E point-septal separation abnormal and the ejection fraction normal (false positives).

Specificity and sensitivity of E point-septal separation: Among the 27 studies in which the E point-septal separation was abnormal, 24 were correctly associated with a reduced radionuclide ejection fraction. Thus, the predictive value of an abnormal E point-septal separation was 89 percent. With regard to sensitivity, 65 percent (24 of 37) of the studies in which the ejection fraction was reduced were identified by an abnormal E point-septal separation. Thirty-three of the 36 studies in which the ejection fraction was normal were identified by a normal E point-septal separation, giving a specificity rate of 92 percent.

Acute myocardial infarction versus previous myocardial infarction: influence of septal motion: In Figure 3 the patients are separated into two groups, those with acute myocardial infarction and those studied late after infarction; their septal motion, as assessed with echocardigraphy, is also noted. Both groups demonstrated an inverse correlation between E

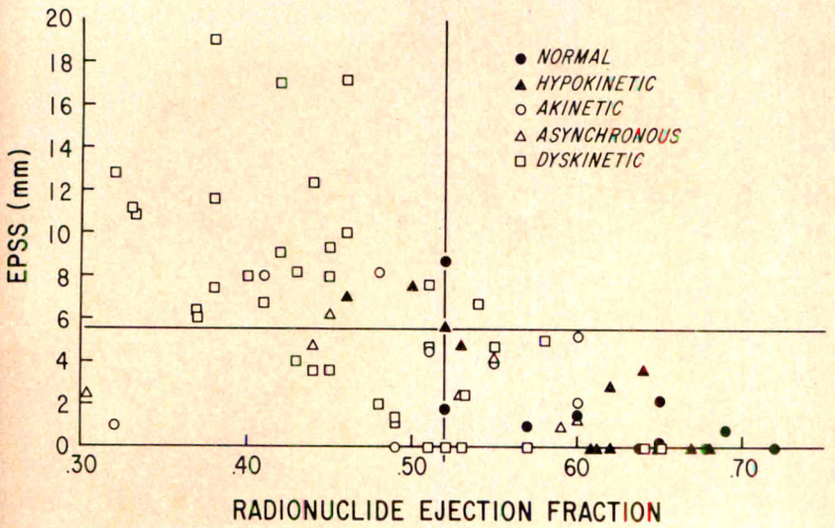


FIGURE 4. Radionuclide ejection fraction is plotted against E point-septal separation (EPSS). The **crossed lines** represent the lower limits of normal for the radionuclide ejection fraction and the upper limits of normal for E point-septal separation. Wall motion abnormalities as assessed with both echocardiography and videotracking are indicated. As can be seen, only 10 patients had no abnormalities with either method. Of the 12 patients with hypokinesia, only 2 had reduced left ventricular performance, whereas the majority of patients with depressed left ventricular function had dyskinesia as the major wall motion abnormality.

point-septal separation and radionuclide ejection fraction. The general distribution of concordant and discordant results did not differ between the two groups. In the group with acute myocardial infarction an abnormal E point-septal separation had a sensitivity rate of 61 percent (14 of 23 studies); the rate was 71 percent (10 of 14) in the group studied late after infarction. This difference was not significant (chi-square analysis). Sixty-one percent of the group with acute infarction had abnormal septal motion compared with 50 percent studied late after infarction. The most common septal motion abnormality was hypokinesia, which occurred in 26 percent of all studies (22 percent in the group with acute infarction and 31 percent in the group studied late after infarction). Hyperkinetic septal motion occurred in 14 percent and was more common in the group with acute infarction (20 percent versus 6 percent). Akinesia occurred in 7 percent of all studies and was also more common in the group with acute infarction (10 percent versus 3 percent). However, none of these differences was significant (chi-square analysis). A dyskinetic septum was present in 10 percent, occurring with equal frequency in the group with acute infarction and the group studied late after infarction.

Further consideration of the relation of E point-septal separation to abnormal wall motion: When all studies were considered, septal motion was normal in 32 studies (44 percent) and abnormal in 41 (56 percent) (Fig. 2). In the group with normal septal motion on echocardiography the sensitivity rate was 73 percent (11 of 15). The group with abnormalities in septal motion had a sensitivity rate of 59 percent (13 of 22). This difference was not significant (chi-square analysis).

Figure 4 identifies the patients by the most severe motion abnormality present from either wall motion videotracking or analysis of echocardiographic septal motion. There were 10 patients who had no abnormalities by either method. In nine of these patients the E point-septal separation and the radionuclide ejection fraction were concordant. Twelve patients had hypokinesia as their most severe free wall or septal motion abnormality. There was concordance in 92 percent (11 of 12) of these patients. In the combined group of patients with either a normal or a hypokinetic free wall or septal motion, or both, there was 91 percent concordance (20 of 22) between E point-septal separation and the radionuclide ejection fraction. In the remainder of the studies with a more severe free wall or septal motion abnormality (akinesia, asynchrony or dyskinesia), there was only 73 percent concordance (37 of 51). In this group with more severe motion abnormalities, the sensitivity rate was 63 percent (22 of 35). Figure 5 shows representative examples of E point-septal separation in patients with and without abnormal septal motion.

Location of infarction: In 40 percent of the studies (29 of 73) the site of infarction as determined from the electrocardiogram was inferior, in 21 percent (15 of 73) it was anterolateral, in 16 percent (12 of 73) it was anterior and in 5 percent (4 of 73) it was lateral. In the remaining 18 percent of studies, the infarction was located in various other sites or combinations of sites or could not be localized. Among these groups, the sensitivity rate ranged from 56 to 71 percent. Although sensitivity was less in the groups with inferior and anterolateral infarctions as compared with the groups with lateral and anterior infarctions, this difference was not significant.

Influence of heart rate on E point-septal separation: Heart rates ranged from 45 to 102 beats/min (mean 71). The influence of heart rate on the E point-septal separation measurement was evaluated with use of partial correlation coefficient analysis. E point-septal separation did not correlate with heart rate ($r_{13} = -0.21$). Although E point-septal separation showed a fair correlation with radionuclide ejection fraction ($r_{12} = -0.69$), the correlation of E point-septal separation with radionuclide ejection fraction when the influence

of heart rate was held constant was not different ($r_{12.3} = -0.70$).

Influence of left ventricular end-diastolic dimension on E point-septal separation: The relation between E point-septal separation and end-diastolic dimension as measured from the echocardiogram is shown in Figure 6. In general, the patients with an enlarged chamber (end-diastolic dimension more than 5.6 cm) had a reduced radionuclide ejection fraction. However, a normal chamber size was associated with a normal as well as a reduced radionuclide ejection fraction. Among the 36 studies in which ejection fraction was normal, end-diastolic dimension was normal in 33 (92 percent). Among the 37 studies where radionuclide ejection fraction was reduced, end-diastolic dimension was normal in 22 (59 percent) and increased in 15 (41

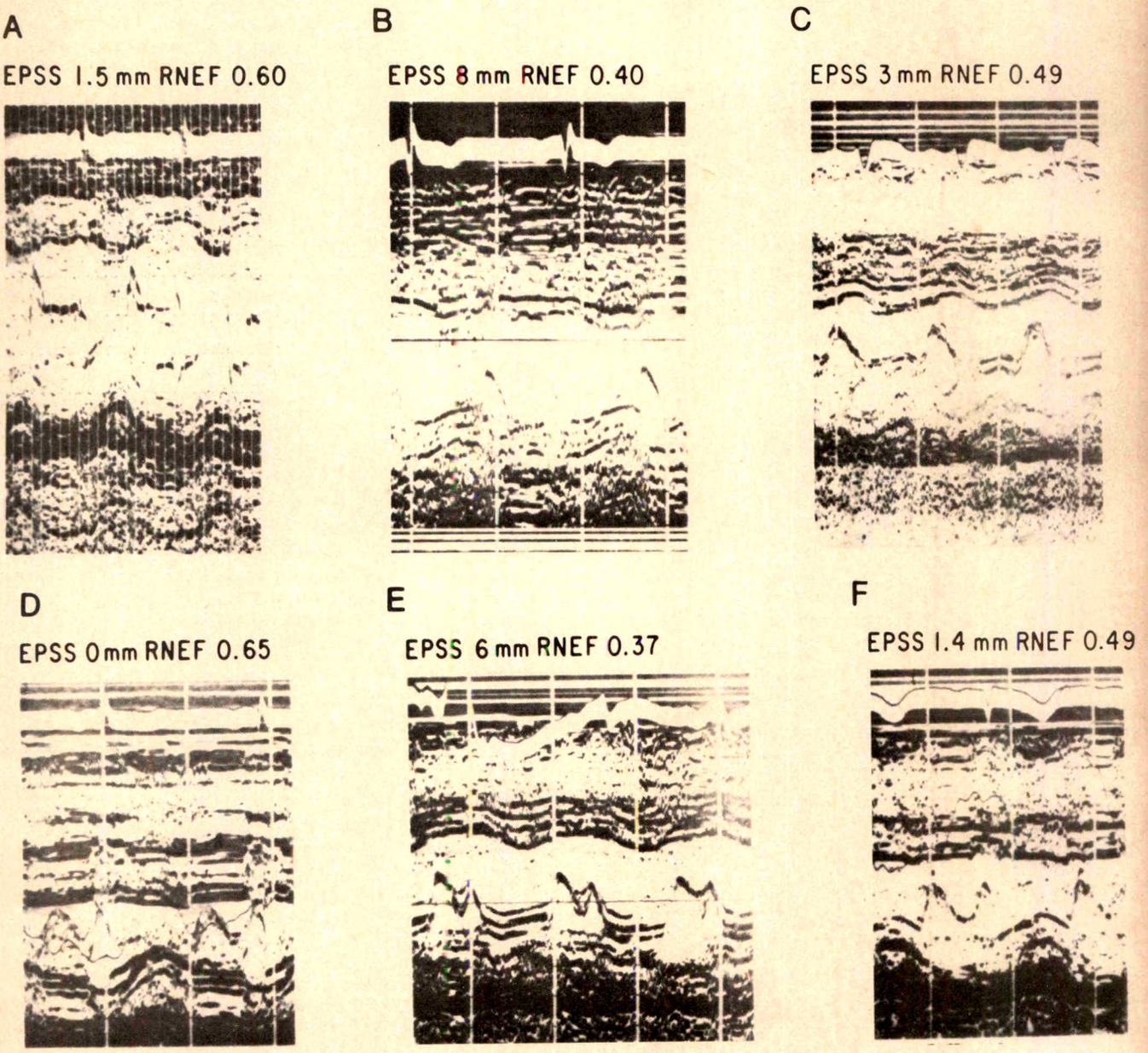


FIGURE 5. Representative examples of the relation of E point-septal separation (EPSS) to the radionuclide ejection fraction (RNEF) in patients with acute myocardial infarction who exhibit both abnormal and normal septal motion. Panels **A, B, D** and **E** show concordance between the ejection fraction and E point-septal separation; panels **C** and **F** show a normal E point-septal separation with a reduced ejection fraction. Abnormal septal motion is evident in panels **D** and **F**. **A**, from a 52 year old man 9 days after inferior infarction; **B**, from a 44 year old man 1 day after anterolateral infarction; **C**, from a 61 year old man 2 days after anterolateral infarction; **D**, from a 70 year old man 4 days after anterolateral infarction; **E**, from a 60 year old woman 2 days after anterior infarction; and **F**, from a 77 year old woman 1 day after anterolateral infarction.

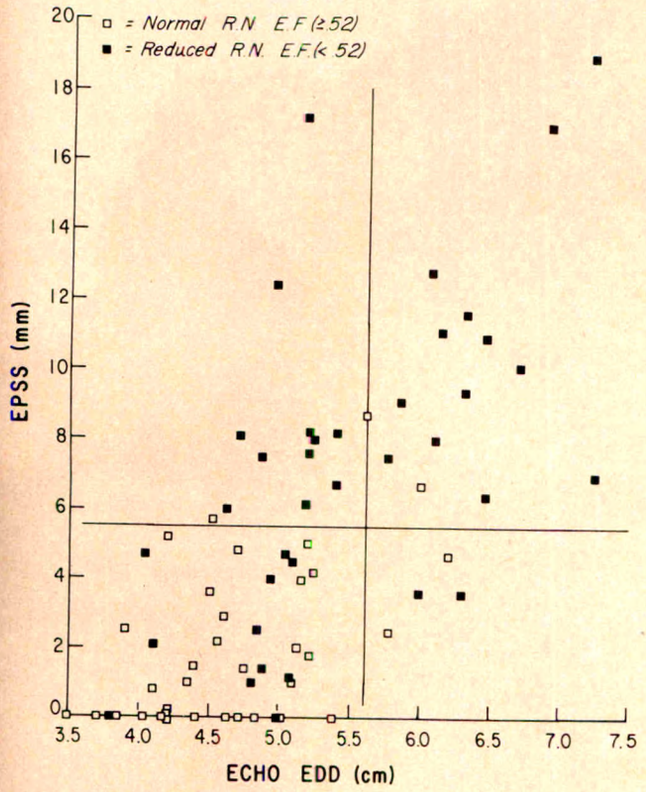


FIGURE 6. The relation of echocardiographic (ECHO) end-diastolic dimension (EDD) to E point-septal separation (EPSS). The **crossed lines** represent the upper limit of normal for end-diastolic dimension and the upper limit of normal for E point-septal separation. There are 12 patients with a normal end-diastolic dimension who have both a reduced radionuclide ejection fraction (R.N. E.F.) and increased E point-septal separation.

percent). Among the studies with a normal E point-septal separation, the end-diastolic dimension was also normal in 91 percent (42 of 46). Among the studies with an abnormal E point-septal separation, this dimension was normal in 48 percent (13 of 27) and increased in 52 percent (14 of 27). Use of a normalized value (E point-septal separation/end-diastolic dimension) did not improve the separation between normal and reduced radionuclide ejection fractions.

Relation of other echocardiographic indexes of left ventricular performance to radionuclide ejection fraction: Other echocardiographic indexes of left ventricular function also were measured and compared with radionuclide ejection fraction. Such a comparison with the percent of fractional shortening is shown in Figure 7A. The patients with a normal radionuclide ejection fraction had a mean percent of fractional shortening of 0.34 ± 0.08 (standard deviation). The percent of fractional shortening was abnormal (less than 0.28)[6] in 25 percent (9 of 36). In the group with a reduced radionuclide ejection fraction the mean percent of fractional shortening was 0.29 ± 0.07. The measure was abnormal in 41 percent (15 of 37). Figure 7B compares the echocardiographic ejection fraction with the radionuclide ejection fraction. In the group with a normal radionuclide ejection fraction the mean echocardiographic ejection fraction was 0.68 ± 0.10. There was an abnormal echocardiographic ejection fraction (less than 0.52) in only 6 percent (2 of 36). In the group with reduced radionuclide ejection fraction echocardiographic ejection fraction had a mean value of 0.62 ± 0.12 and was abnormal in only 14 percent (5 of 37). Figure 7C compares the radionuclide ejection fraction with the echocardiographic mean rate of diameter

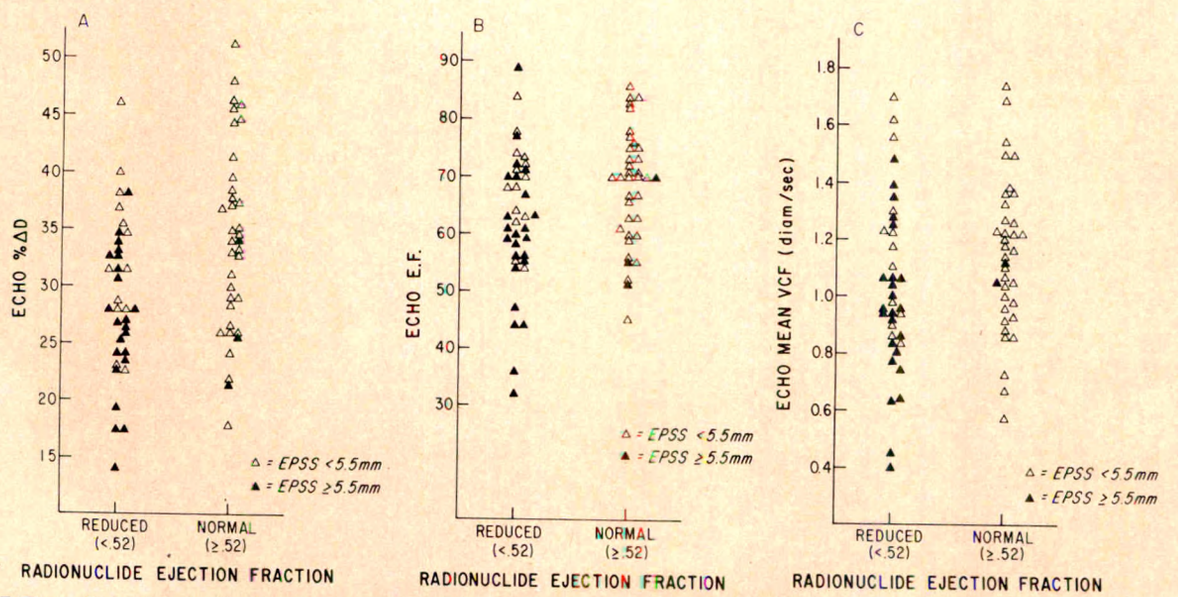


FIGURE 7. The radionuclide ejection fraction is plotted against other echocardiographic (ECHO) measures of left ventricular performance. For discussion, see text. diam = diameters; E. F. = ejection fraction; EPSS = mitral valve E point-septal separation; mean VCF = mean rate of internal diameter shortening; % ΔD = percent of fractional shortening.

shortening (mean Vcf). In the group with a normal radionuclide ejection fraction the echocardiographic mean Vcf had an average value of 1.15 ± 0.27 diameters/sec and was abnormal (less than 1.00 diameters/sec)[6] in 28 percent (10 of 36). In the group with a reduced ejection fraction the echocardiographic mean Vcf had a mean value of 1.03 ± 0.30 and was abnormal in 51 percent (19 of 37). The ability of various echocardiographic indexes of left ventricular performance to separate patients with a normal ejection fraction from those with a reduced ejection fraction is shown in Tables I and II. As can be seen, E point-septal separation is superior to the other echographic measures.

TABLE I

Relation of Radionuclide Ejection Fraction to Echocardiographic Indexes of Left Ventricular Performance

	Radionuclide Ejection Fraction		Chi-Square (χ^2) Analysis
	Normal	Reduced	
EPSS			
Normal	33 (TN)	13 (FN)	$\chi^2 = 22.65$
Abnormal	3 (FP)	24 (TP)	$P < 0.00005$
%ΔD			
Normal	27 (TN)	22 (FN)	$\chi^2 = 1.354$
Reduced	9 (FP)	15 (TP)	P = NS
Mean Vcf			
Normal	26 (TN)	18 (FN)	$\chi^2 = 3.307$
Reduced	10 (FP)	19 (TP)	P = NS
Ejection Fraction			
Normal	34 (TN)	32 (FN)	$\chi^2 = 0.573$
Reduced	2 (FN)	5 (TP)	P = NS

EPSS = E point-septal separation; FN = false negatives; FP = false positives; Mean Vcf = mean rate of internal diameter shortening; NS = $P > 0.05$; P = probability; %ΔD = percent of fractional shortening; TN = true negatives; TP = true positives.

TABLE II

Specificity, Sensitivity and Predictive Value of E Point-Septal Separation and Other Electrocardiographic Measures of Left Ventricular Performance

	Specificity Rate (%)	Sensitivity Rate (%)	Predictive Value (%)
EPSS	92	65	89
%ΔD	64	41	63
Mean Vcf	72	51	66
Ejection fraction	94	14	71

EPSS = E point-septal separation; %ΔD = percent of fractional shortening; Mean Vcf = mean rate of internal diameter shortening.

Discussion

Previous ultrasonic studies in patients with acute myocardial infarction: It is well recognized that patients with coronary artery disease and myocardial infarction pose special problems in M mode echocardiographic assessment of left ventricular performance,[11,12] and only a few such studies have been reported. Corya et al.[13] reported a relation between the left ventricular internal dimension and clinical heart failure in patients with acute myocardial infarction. Nieminen and Heikkila[14–16] published a series of echocardiographic studies in 30 patients with acute myocardial infarction. A site of asynergy, which correlated with the site of infarction, could be found in all patients. Serial records were used to follow the end-diastolic dimension, ejection fraction and mean rate of diameter shortening (Vcf), which were abnormal in all patients. The echocardiographic indexes tended to improve in most patients 2 to 3 days after infarction. These investigators[16] also examined wall motion amplitude and observed that the echocardiographic site of asynergy also was most severely affected within the first 3 days.

Usefulness and limitations of the E point-septal separation measurement: To date there have been no studies in which a simple echocardiographic measure of left ventricular performance has been correlated with totally independent noninvasive techniques for measuring left ventricular function and wall motion. Previously, E point-septal separation has been proposed as a useful index of left ventricular function.[1] Therefore, we decided to assess E point-septal separation in patients with acute and previously documented myocardial infarction. Our data indicate that an increased E point-septal separation is a highly specific finding, identifying a reduced radionuclide ejection fraction in 92 percent of studies. By contrast, the sensitivity of abnormal E point-septal separation was 65 percent; therefore, in a sizable proportion (35 percent) of studies a reduced radionuclide ejection fraction was not detected by abnormal E point-septal separation. However, because of overlap, normal values for E point-septal separation were found to be less useful. These results are consistent with the observations of Massie et al.[1] regarding the utility of an increased E point-septal separation, but they do not support their contention that normal E point-septal separation is usually associated with normal left ventricular performance.

Influence of heart rate and size on E point-septal separation: The influence of heart rate on E point-septal separation was examined using partial correlation coefficients, but this analysis failed to demonstrate any significant influence. When the influence of the heart rate was kept statistically constant, this did not improve the correlation of E point-septal separation with the radionuclide ejection fraction (r −0.69 versus −0.70). The size of the left ventricle as reflected by the echocardiographic end-diastolic dimension had some influence on the E point-septal separation measurement. However, end-diastolic dimension was clearly not the sole influence on E point-septal separation because only 52 percent of those with abnormal E point-septal separation had an abnormal end-diastolic dimension. The remaining 48 percent had a normal end-diastolic dimension associated with abnormal E point-septal separation. Because end-diastolic dimension is not the primary factor in E point-septal separation measurements, it is not surprising that division ("normaliza-

tion") of E point-septal separation by end-diastolic dimension did not improve the separation between patients with normal and reduced radionuclide ejection fraction. Similarly, the product of these two measures was not useful in improving separation.

Relation of E point-septal separation to other ultrasonic measures of left ventricular function: The other echocardiographic indexes of left ventricular function were not useful alone or as an adjunct to the E point-septal separation measurement. Thus, the percent of fractional shortening (% ΔD), echo mean rate of diameter shortening (Vcf) and echocardiographic ejection fraction all showed considerable overlap when the group with normal radionuclide ejection fraction was compared with the group with a reduced ejection fraction (Fig. 7; Tables I and II). This observation is consistent with previously reported findings concerning the limitations of these echocardiographic indexes in patients with coronary artery disease or myocardial infarction.[17] By contrast, E point-septal separation was far more accurate in discriminating between patients with a normal and a reduced radionuclide ejection fraction (Tables I and II).

Relation of E point-septal separation to abnormal wall motion: Combining echocardiography with wall motion videotracking allowed assessment both of septal motion and of the motion of the lateral, anterior and posterior left ventricular surfaces. In the 22 patients who had no detectable wall or septal motion abnormalities or who had only hypokinesia, E point-septal separation correctly separated 91 percent of these patients with a normal and a reduced radionuclide ejection fraction; that is, there was 91 percent concordance. In the group with qualitatively more severe motion abnormalities (akinesia, asynchrony or dyskinesia) there was only 73 percent concordance. Thus, E point-septal separation seems to be useful for separating normal from reduced radionuclide ejection fraction when a less severe wall motion abnormality (hypokinesia) is present. All but 2 of 22 patients in this group had a normal radionuclide ejection fraction, and this is consistent with the relatively modest abnormal wall motion they exhibited. In the group with more severe wall motion abnormalities, the false negative rate was 37 percent. In all 13 of the false negative studies (normal E point-septal separation with reduced radionuclide ejection fraction) qualitatively more severe abnormalities were present. When the echocardiogram was considered alone, only three patients had a dyskinetic septum, four had a normal septum and four had a hypokinetic septum, yet all had more severe wall motion abnormalities as detected by videotracking.

Possible mechanisms for abnormal E point-septal separation: The relation of a purely diastolic event, separation or apposition of the E point of the mitral valve to the interventricular septum, to alterations in left ventricular systolic function requires explanation. The mechanism of this relation is uncertain, but E point-septal separation appears to be a complex function of mitral valve, interventricular septal and left ventricular free wall motion. In some patients, increased chamber size plays an important role in determining the magnitude of E point-septal separation. In experimental studies, it has been reported that an average of 17.6 percent of total mitral filling volume passes across the valve by the time of complete valve opening.[18] DeMaria et al.[19] documented a considerable reduction in early diastolic flow in patients with coronary artery disease. Such reduction in early diastolic flow coupled with alterations in left ventricular end-diastolic pressure, which are common in patients with ischemic heart disease and which can produce alterations in mitral valve motion,[20] may contribute importantly to the abnormal E point-septal separation observed in the majority of patients with a reduced ejection fraction. Abnormalities of wall motion also may influence the position of the mitral valve at the end of systole. When the valve does open, the position of the E point of the anterior leaflet may be "inappropriately" close to the septum because of the abnormal wall motion during systole. This and other factors such as papillary muscle dysfunction may contribute to the large percent of false negative results in patients with reduced left ventricular function and more severe abnormalities in left ventricular wall motion.

Implications: An abnormal E point-septal separation (more than 5.5 mm) was found to be highly specific (92 percent) for a reduced radionuclide ejection fraction in our study population of patients with acute or old myocardial infarction. Sensitivity was less, 65 percent of patients with a reduced radionuclide ejection fraction exhibiting abnormal E point-septal separation measurements. False negative results occurred primarily in patients with abnormalities of left ventricular wall motion. A reduced radionuclide ejection fraction occurred in 28 percent of patients with normal E point-septal separation. Abnormal E point-septal separation was considerably more accurate than other echocardiographic indexes of left ventricular function in identifying patients with a reduced radionuclide ejection fraction. It should be emphasized that measurement of E point-septal separation requires only visualization of the mitral valve and interventricular septum, which can be achieved in virtually all patients. Simultaneous visualization of the interventricular septum and the posterior left ventricular wall, necessary for most other functional measurements, is not required; nor is it necessary to measure the left ventricular ejection time either from the echogram or from the indirect carotid arterial pulse tracing.

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Significance of Changes in R Wave Amplitude During Treadmill Stress Testing: Angiographic Correlation

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Coronary angiograms and treadmill stress tests were reviewed in 89 patients. Changes in R wave amplitude were measured in the control and immediate postexercise periods. Of 45 patients with normal coronary arteries, 41 (91 percent) had a decrease in R wave amplitude ($P < 0.01$); 3 (7 percent) had an increase in amplitude, including 2 with abnormal left ventriculograms. The remaining patient (2 percent) had abnormal wall motion but no change in R wave amplitude.

Among the 44 patients with significant coronary artery disease (70 percent or greater luminal narrowing in one or more vessels), R wave amplitude increased after exercise in 26 (59 percent) with more severe coronary artery disease. R wave amplitude decreased in 18 patients (41 percent) with normal or minimally abnormal resting ventriculograms and less severe coronary artery disease ($P < 0.01$).

Changes in R wave amplitude reflect ventricular function, an increase in R wave amplitude reflecting more severe dysfunction and severe coronary narrowing. A decreased R wave amplitude indicates normal or minimal dysfunction and is strongly associated with normal coronary angiograms.

S-T segment depression with exercise is well recognized as a frequent indicator of myocardial ischemia. Changes in R wave amplitude have been reported by several investigators in experimental studies[1–6] and have been shown to occur with exercise in normal subjects[7–13] and patients with coronary artery disease.[9,14,15] Millard et al.[16] found that, after experimental total inflow occlusion or hemorrhage, the early QRS radially oriented vectors decreased whereas the later vectors increased. Occlusion of the outflow tract with a resultant increase in left ventricular volume had the opposite effect. Millard et al. considered their results consistent with the so-called Brody effect.[17] If exercise-induced changes in R wave amplitude indeed reflect left ventricular function,[13,18] the informative value of a treadmill stress test would be enhanced. We therefore undertook this study to correlate R wave amplitude during treadmill stress testing with left ventricular function and the degree of coronary arterial obstruction.

Material and Methods

Patients: Treadmill stress test records and coronary angiograms of patients referred for evaluation of chest pain were reviewed retrospectively. Of the 89 patients, 45 (32 men and 13 women) had normal coronary angiograms, defined as no occlusion or less than 30 percent cross-sectional narrowing. The patients' ages ranged from 35 to 65 years (mean 50). The remaining 44 patients (35 men and 9 women) had significant coronary artery disease, defined as greater than 70 percent cross-sectional narrowing. Their ages ranged from 37 to 71 years (mean 54). Patients with cardiac valve disease, cardiomyopathy, conduction defects, premature ventricular complexes or hypertension and those taking digitalis, beta adrenergic blocking agents, nitroglycerin or diuretic drugs were excluded.

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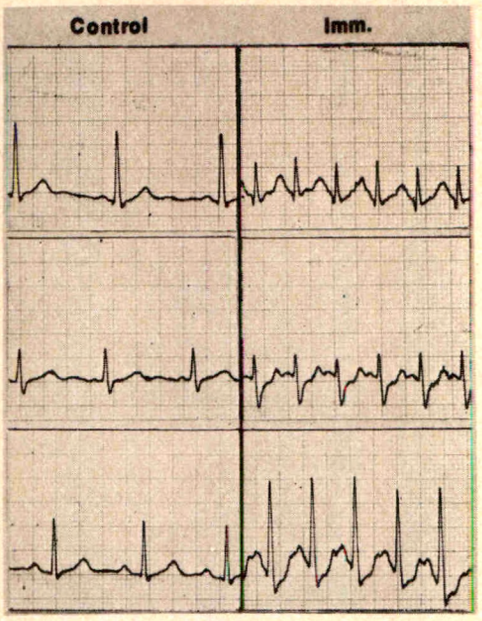


FIGURE 1. Changes in R wave amplitude after exercise in three patients. **Top,** decreased R wave amplitude in a patient with normal coronary arteries. **Middle,** decreased R wave amplitude in a patient with coronary artery disease. **Bottom,** increased R wave amplitude in a patient with coronary artery disease. Imm. = immediate postexercise period.

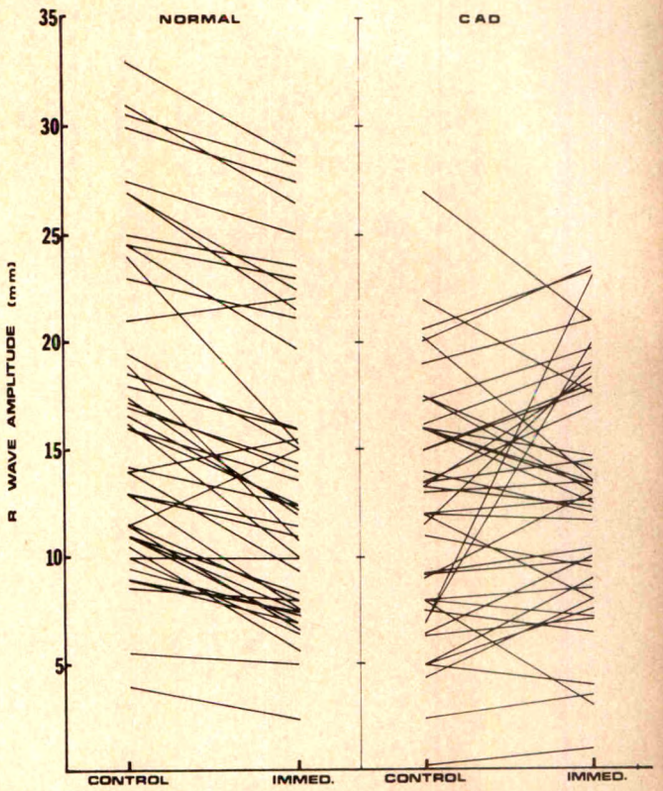


FIGURE 2. Changes in R wave amplitude after exercise in subjects with normal coronary angiograms and in patients with coronary artery disease (CAD). R wave amplitude decreases in most of the normal subjects but increases or decreases in the subjects with coronary disease depending on the severity of the disease. IMMED. = immediate postexercise period.

Treadmill stress tests: The interval between treadmill stress testing and coronary angiography was 1 to 20 days in all but 6 patients in whom the interval was 2 to 5 months. Patients underwent a progressive maximal exercise stress test according to the Ellestad protocol[19–21] using three leads (CM_5, a vertical bipolar lead and a unipolar V_1 lead). Significant S-T segment depression was defined as 1 mm S-T depression below the resting level 60 msec from the J point if the depression was horizontal or flat and 1.5 mm depression 80 msec from the J point if the depression was upsloping during exercise or in the immediate postexercise period.[19] We found the difference in the R wave amplitude between the control periods during standing and sitting was less than 0.5 mm. The R wave was measured in the CM_5 lead only; the period immediately after exercise with the patient still standing was compared with the sitting control period. The three electrocardiographic leads were monitored continuously during and after exercise. A 10 mm/mv calibration standard was used. The R wave amplitude was measured from the isoelectric line to the peak of the R wave in mm for 6 to 15 beats (average 10). No beats with prolonged conduction were included in the measurement of R wave amplitude. The average value was used in the study to minimize respiratory variations. The treadmill stress test was examined independently without prior knowledge of the coronary angiogram.

Left and right heart catheterization and coronary angiography: These procedures were performed using the Sones or Judkins technique. No patient had evidence of heart failure during the study. Coronary angiography was performed using 35 mm film with multiple views. Single plane left ventricular angiography was performed in the right anterior oblique projection. The criterion for a diagnosis of coronary artery disease was luminal stenosis greater than 70 percent of one or more coronary arteries. The coronary arteries were separated into branches according to the reporting system of the American Heart Association.[22] The left ventricular angiogram was divided into five segments: (1) posterobasal, (2) diaphragmatic, (3) apical, (4) anterolateral, and (5) anterobasal. Areas with an abnormal contraction pattern were described qualitatively as hypokinetic when systolic movement was less than normal, akinetic when no movement was observed during systole and dyskinetic when paradoxical systolic movement was seen.

The coronary anatomy and left ventricular angiogram were graded without prior knowledge of the treadmill stress test results. Exercise electrocardiograms and angiograms were read by two independent observers, and any discrepancies were resolved by a third observer.

Results

Normal Coronary Angiograms

Of the 45 patients with normal coronary angiograms, 41 (91 percent) had a decrease in R wave amplitude of -3.4 mm $\pm$ 0.3 (mean $\pm$ standard error of the mean), with a range of -0.5 to -8.7 mm. This change was statistically significant ($P < 0.01$). In the remaining four patients, the R wave amplitude increased by 3.5, 1.0 and 1.5 mm, respectively, in three patients (7 percent) and showed no change in one patient (2 percent) (Fig. 1A and 2; Table I).

The postexercise S-T segments showed no depression in 27 of the 45 patients (60 percent). Seven patients (16 percent) had equivocal S-T segment changes, and 11 (24 percent) had significant depression; the latter represent

TABLE I

Changes in R Wave Amplitude in the Two Patient Groups

R Wave Amplitude	Normal	CAD	Total
Decrease	41	18	59
Increase	3	26	29
No change	1	. . .	1
Total	45	44	89

P (probability) <0.01.
CAD = coronary artery disease.

the false positive group. Nine of these 11 patients had decreased R wave amplitude.

Abnormal Coronary Angiograms

Increased R wave amplitude: Of the 44 patients with abnormal coronary angiograms, 26 (59 percent) had an increase in R wave amplitude that averaged +3.4 ±0.7 mm (range +0.5 to +16 mm) (Fig. 1C and 2; Table I). The change in R wave amplitude was significant (P <0.01).

The postexercise S-T segments showed significant depression in 13 of the 26 patients (50 percent), equivocal depression in 3 (12 percent) and no depression in 10 (38 percent).

Coronary angiography revealed that 3 of the 26 patients (12 percent) had single vessel disease, 8 (31 percent) had two vessel disease and 15 (58 percent) had three vessel disease. The number of branches of significantly occluded coronary arteries were as follows: occlusion in a single arterial branch, 3 patients (12 percent); in two branches, 6 patients (23 percent); in three branches, 6 patients (23 percent), and in four or more branches, 11 patients (43 percent).

Decreased R wave amplitude: Of the 44 patients with abnormal angiograms, 18 (41 percent) had a decrease in R wave amplitude immediately after exercise. This decrease averaged −2.7 ± 0.4 mm (range −0.5 to −6.7). The change is significant (P <0.01) (Fig. 1B and 2; Table I). The postexercise tracings showed significant S-T depression in 7 of the 18 patients (39 percent) and equivocal depression in 5 (28 percent); 6 patients (33 percent) showed no change. Of the 18 patients, 23 (67 percent) were classified as having an abnormal treadmill stress test on the basis of significant S-T depression or typical chest pain, 4 (22 percent) as having an equivocal test and 2 (11 percent) as having a normal test.

Coronary angiography revealed that 8 of the 18 patients (45 percent) had single vessel disease, 6 (33 percent) had two vessel disease and 4 (22 percent) had three vessel disease. The number of occluded branches was as follows: occlusion in one branch, 6 patients (33 percent); in two branches, 6 patients (33 percent); in three branches, 3 patients (17 percent), and in four or more branches, 3 patients (17 percent).

The group with an increase in R wave amplitude had two or three vessel disease, whereas the group with a decreased amplitude had one or two vessel disease (Fig. 3); this difference was significant (P <0.05). The group with an increase in R wave amplitude also had more diseased branches than the group with a decrease in amplitude (Fig. 4).

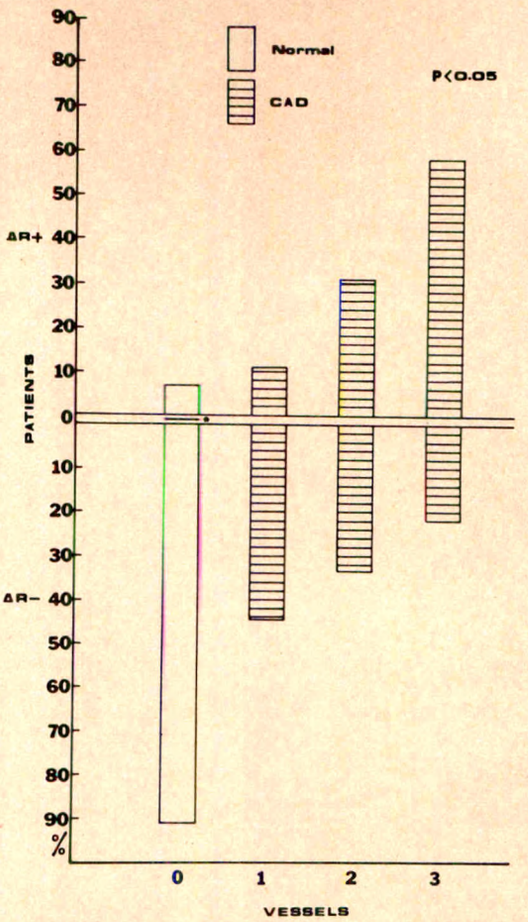


FIGURE 3. Changes in R wave amplitude plotted against the severity of coronary artery disease. In patients with no or one vessel disease R wave amplitude decreases, but in those with two or three vessel disease it increases. CAD = coronary artery disease; ΔR+ = increase in R wave amplitude; ΔR− = decrease in R wave amplitude; P = probability; —* = one patient with no change in R wave amplitude.

R Wave Changes and Left Ventriculography

Normal left ventriculograms: All 41 patients with a normal left ventriculogram had a decrease in R wave amplitude. Of the three patients with normal coronary arteries but an increase in R wave amplitude on the stress test, two had segmental contraction abnormalities on left ventricular angiography, and one had no abnormalities. One patient had apical and anterolateral hypokinesia; another had diaphragmatic and apical akinesia and anterolateral hypokinesia. One patient with no changes in R wave amplitude had apical and anterolateral wall hypokinesia.

Increased R wave amplitude: Of the 26 patients with an increase in R wave amplitude and coronary artery disease, 7 (27 percent) had no segmental abnormalities. Three of the 26 patients (12 percent) had one

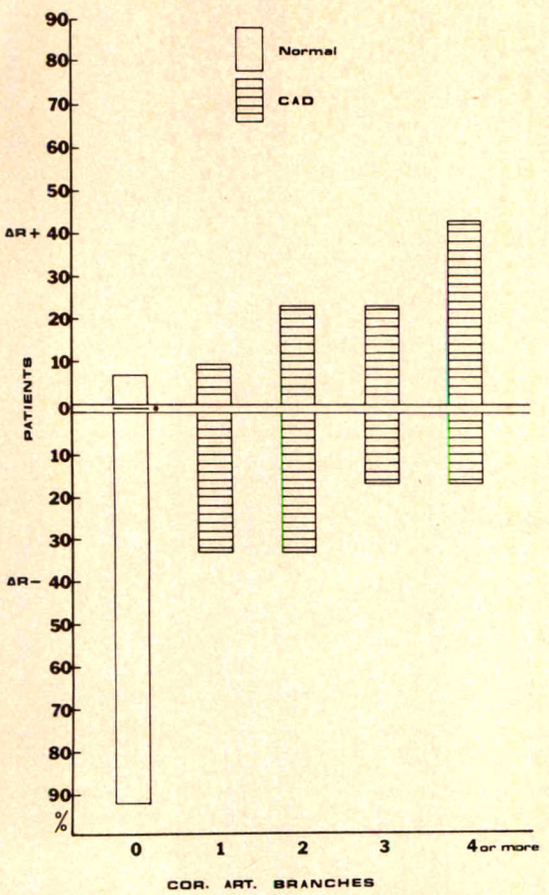


FIGURE 4. Changes in R wave amplitude plotted against the number of diseased branches of the coronary arteries (COR. ART.). Patients with an increase in R wave amplitude have more diseased branches. Abbreviations as in Figure 3.

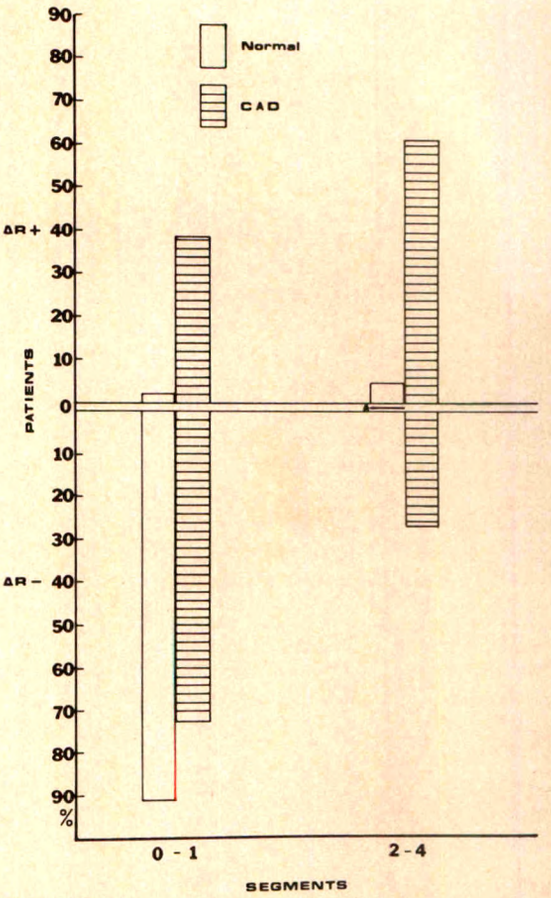


FIGURE 5. Changes in R wave amplitude correlated with segmental abnormalities on ventriculography. The group with decreased R wave amplitude tended to have no or one segment of abnormal wall motion; the group with increased amplitude had two or more segments of abnormal wall motion. Abbreviations as in Figure 3.

abnormal segment, 4 (15 percent) had two abnormal segments, 10 (39 percent) had three abnormal segments and 2 (7 percent) had four abnormal segments.

Decreased R wave amplitude: Of the 18 patients with a decrease in R wave amplitude and coronary artery disease, 8 (45 percent) had no segmental contractile abnormalities on left ventricular angiography. Five patients (28 percent) had only one segment of abnormal contraction, four (22 percent) had three abnormal segments and one (5 percent) had four abnormal segments.

Figure 5 compares the number of segmental abnormalities with changes in R wave amplitude. In the group with increased amplitude, 38 percent of patients had no or one segment of abnormal wall motion, and 62 percent had two or more segments of abnormal motion. In the group with decreased amplitude, 72 percent of patients had no or one segment of abnormal wall motion, and 28 percent had two or more abnormal segments. The group with an increase in R wave amplitude had more segmental contraction abnormalities in the control left ventricular angiograms than the group with a decrease in amplitude.

Discussion

In 1956, Brody[17] postulated that, because of the radial orientation of left ventricular electromotive forces, QRS amplitude would increase as left ventricular blood mass increases. Conversely, as left ventricular blood mass decreases, QRS amplitude would decrease. This has been labeled the Brody effect. Subsequently, the influence of intracardiac blood mass on QRS amplitude has been studied and verified in animal experiments, mathematic studies and experimental models[1–6,16,23–26]; however, controversy persists. Some studies[1,13] indicate that QRS amplitude is related primarily to contractility, whereas other studies[2,13] indicate that volume load is the determining factor. Digitalis increases R wave amplitude, but the mechanism of action remains controversial.[1,2,13]

A reduction in R wave amplitude with exercise stress testing in normal persons was reported by several investigators.[7,8,11–13] Lepeschkin[27] postulated that the reduction was due to an augmented atrial repolarization wave. However, Simoons and Hugenholtz[10] reported that this was not the primary factor.

To date, there have been no reports on an increase in R wave amplitude with exercise. Ellestad[19] noted that in patients with coronary disease and a positive treadmill stress test, the R wave decreased less than in normal patients.[15] Lloyd-Thomas[9] noted that of 187 patients with coronary disease, only 9 had a decrease in R wave amplitude with exercise stress testing. Kentala and Luurila,[18] while studying the effect of exercise training, suggested that changes in R wave amplitude may correlate with left ventricular function.

Left ventricular volumes during tachycardia, exercise and ischemia: In patients with coronary artery disease and pacemaker-induced tachycardia to the point of ischemia, the left ventricular systolic and diastolic volumes were observed to increase rather than decrease as is normal with atrial pacing.[28–33] Sharma et al.[29] demonstrated an increase in left ventricular volume with angina induced by leg raising exercise during cardiac catheterization. This finding can be explained by a transient impairment of left ventricular function due to ischemia, which is well documented in man,[30,34–36] in intact experimental heart preparations and in isolated papillary muscle studies.[37–40] Decreased left ventricular volume with ischemia after handgrip exercise was also reported.[41] Several studies[28,32–34,41–43] noted a decrease in left ventricular volume in pacemaker- or exercise-induced tachycardia in patients with normal coronary arteries.

Cardiac output during exercise is affected by tachycardia, sympathetic activity and the Frank-Starling mechanism.[43,44] During exercise, tachycardia and increased sympathetic activity are the primary mechanisms for the decrease in left ventricular volume, and the Frank-Starling mechanism is overidden by these factors.[43] In patients with coronary artery disease, the sympathetically mediated reduction in heart size appears to be minimized because of decreased contractility as well as localized asynergy or hypokinesia. Therefore, the systolic volume is larger than in the normal patient. The replacement of the myocardium by scar tissue and the compliance changes seen with ischemia may also have an effect.[31,34,45–49] Therefore, the increased left ventricular volumes in systole and diastole result in an increase in R wave amplitude according to the Brody effect.

Correlation of postexercise R wave amplitude, coronary artery disease and left ventricular dysfunction: In our study, the group of patients with decreased R wave amplitude after exercise had less severe coronary artery disease and fewer wall motion abnormalities. The reduced R wave amplitude after exercise in patients with coronary disease suggests the possibility that a compensatory hypercontractility of the normal areas of myocardium counterbalances the reverse effect in ischemic areas and that left ventricular volume therefore remains reduced.[33] The patients with increased R wave amplitude after exercise who had more severe coronary artery disease and more wall motion abnormalities had left ventricular dysfunction to a degree that cannot be compensated for by this mechanism, and the left ventricular volumes consequently increased.

In our series, 91 percent of patients with normal coronary arteries had a decrease in R wave amplitude with exercise, and only three patients had an increase. Two of these patients had evidence of segmental abnormalities in the left ventricular angiogram indicating left ventricular dysfunction.

Of the patients with angiographically proved coronary artery disease, 59 percent had an increase in R wave amplitude, and 41 percent had a decrease with exercise. The patients with a decrease in R wave amplitude had primarily one or two vessel disease, and those with an increase in R wave amplitude had two or three vessel disease. In fact, 57 percent of the group with an increase in R wave amplitude had three vessel disease.

Left ventricular angiography revealed no or one segment of abnormal motion in 72 percent of the group with reduced R wave amplitude and in only 38 percent of the group with increased amplitude; 62 percent of the latter had more than two segments of abnormal motion. These left ventriculograms were performed while the patients were in a control state and not experiencing angina or ischemia; had they been performed with pacemaker- or exercise-induced angina or ischemia, it is likely that we, as have others,[30,34,41] would have observed more segments with abnormal motion. Such studies might have disclosed increased left ventricular volume in the patients with three vessel disease and minimal or no further areas of abnormal motion and minimal or no further increase in left ventricular volume in patients with single vessel disease.[29,30,41]

Implications: Our findings suggest that a decrease in R wave amplitude during exercise stress testing implies normal or only minimally impaired left ventricular function and is usually seen in subjects with normal coronary arteries or mild to moderate coronary artery disease. An increase in R wave amplitude during stress testing suggests significantly impaired left ventricular function with elevated ventricular systolic and diastolic volumes and pressures and is more likely to be associated with severe coronary arterial narrowing.

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Correlative Studies of Serum Digitalis Levels and the Arrhythmias of Digitalis Intoxication

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Correlative studies of serum digoxin levels, cardiac rhythm and related clinical laboratory data were carried out in 114 patients. Seventy-three patients who presented with 79 episodes of arrhythmias typical of digitalis intoxication could be separated into a normokalemic group of 55 patients whose serum digoxin level was 3.68 ± 0.17 ng/ml (mean ± standard error of the mean), and a hypokalemic group of 24 with a mean serum digoxin level of 1.13 ± 0.04 ng/ml ($P < 0.001$). Of 45 consecutive normokalemic patients with a high serum digoxin level (more than 2 mg/ml) who underwent serial studies, 17 had arrhythmias. Serial studies in 10 hypokalemic patients revealed an inconsistent relation between presence of arrhythmia and serum digoxin level. During repletion of serum potassium in seven of these patients with an arrhythmia, the arrhythmia disappeared without a significant change in serum digoxin level in four patients. A group of seven patients had 16 episodes of serum digoxin level greater than 2.2 ng/ml, but an arrhythmia occurred during only 3 of these episodes. A sharp border between toxic and therapeutic serum digoxin values was not found in these groups of study patients. The serum digoxin level at which arrhythmias occurred appeared to be variable for both groups and individual patients. However, correlative studies utilizing serum digoxin levels can define existing thresholds for therapeutic and toxic effects and may often be more useful than isolated observations.

The brilliant discovery of precise methods for determining digitalis glycoside levels in serum or plasma[1–3] has led to continuing controversy concerning their value in the diagnosis of digitalis toxicity.[4–8] It was emphasized early that serum glycoside levels should be used as one bit of the contributing clinical data.[2,3] Butler and Lindenbaum[9] recently classified subsets of patients as sensitive, that is, showing toxic effects at "therapeutic" concentrations, as opposed to those demonstrating toxicity at levels above the so-called therapeutic range. A rigorous but theoretical analysis of data from selected publications[10] found the serum glycoside level unproved as an independent diagnostic test of digitalis toxicity.

The value of measuring serum glycoside levels in the investigation and clinical management of patients has been impressively documented.[4,9] Careful clinicians have for a long time commented on apparent variations in sensitivity to "usual" doses of various glycosides.[11] Therefore, it should not be unexpected to encounter signs of glycoside intoxication at a spectrum of serum values. In fact, a poor relation between serum glycoside values and tolerance to an infusion of acetylstrophanthidin has been reported.[5,12] It may be more reasonable to utilize serum glycoside concentration in relation to cardiac response as an index of myocardial tolerance of glycosides rather than to consider it a precise diagnostic test of therapeutic adequacy or of toxicity.

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TABLE I

Summary of Data* From 73 Patients Presenting With Arrhythmias Associated With Digoxin Intoxication and Classified Into Normokalemic and Hypokalemic Groups

	Normokalemic (Serum K^+ >3. 5 mEq/liter)	Hypokalemic (Serum K^+ <3.5 mEq/liter)	*P*
Patients (no.)	55	24	
Age (yr)	63.5 ± 1.7	62.2 ± 2.2	NS
Serum K^+ (mEq/liter)	4.73 ± 0.08	3.02 ± 0.06	<0.001
Blood urea nitrogen (mg/100 ml)	35.1 ± 3.6	24.6 ± 3.0	NS
Serum digoxin level (ng/ml)	3.68 ± 0.17	1.13 ± 0.14	<0.001
Incidence of arrhythmias (%)			
Ventricular ectopic activity	60	75	
PAT with block	12.7	12.5	
AF <50/min	10.9	none	
A-V dissociation	9.1	12.5	
Junctional rhythm	7.3	none	

* Mean ± standard error of the mean.
AF = atrial fibrillation; A-V = atrioventricular; NS = not significant; *P* = probability; PAT = paroxysmal atrial tachycardia.

This report describes various correlative investigations carried out during the past several years: (1) studies in patients presenting to our laboratory with arrhythmias typical of digitalis intoxication, (2) serial observations in a nearly consecutive series of normokalemic patients discovered to have high serum glycoside levels, (3) serial studies in hypokalemic patients with arrhythmias taking glycosides who underwent correction of potassium deficiency, and (4) studies in individual patients who inadvertently experienced two or more distinct rises in serum glycoside level above the "therapeutic" range. The results of these observations indicate that the serum glycoside level determination is moderately specific but has poor predictive accuracy for the diagnosis of digitalis intoxication.

Methods

The studies were performed in a total of 114 patients, all middle-aged male veterans with heart disease who had previously been digitalized and who had been taking maintenance doses of digoxin (108 patients) or digitoxin (6 patients). The most frequent diagnosis was congestive heart failure secondary to ischemic heart disease with or without hypertension. Rheumatic heart disease, isolated atrial fibrillation and cor pulmonale were infrequent. Modest obstructive bronchopulmonary disease without significant blood gas and arterial pH abnormality was a common secondary diagnosis.

1. Digitalized patients with arrhythmias typical of digitalis intoxication: Data were obtained on 79 occasions from 73 consecutive patients who presented to the hospital with arrhythmias typical of digitalis intoxication and who gave a clear history of digoxin ingestion (Table I).

The arrhythmias and conditions required for this diagnosis were: (1) supraventricular tachycardia with heart block, (2) frequent (more than 5/min) or multifocal ventricular premature beats or ventricular tachycardia, (3) atrial fibrillation with ventricular response less than 50/min and ventricular premature beats, and (4) second or third degree atrioventricular block. Additionally, the patient had to have been taking digoxin or digitoxin before the onset of arrhythmia with disappearance of the rhythm disturbance when the glycoside was withheld.[2–4] Blood sampling was carefully timed so that it followed the last known dose of glycoside by at least 6 and usually 24 hours but not longer.[13,14]

2. Serial observations in patients with elevated serum digitalis concentrations or patients suspected of digitalis intoxication, or both: A total of 63 serial studies were carried out in 62 patients, 21 of whom were initially observed under protocol 1. Within this group, insofar as possible, all consecutive normokalemic patients (45 patients) found to have glycoside levels above 2 ng/ml were studied for approximately 6 months. They were studied until the serum glycoside level returned to the therapeutic range and, to rule out other arrhythmogenic influences, until any associated arrhythmia disappeared within 24 hours of return of serum level to therapeutic range. A small number of patients during this time could not be studied because of discharge from the hospital, death or failure to volunteer. Other subsets in this series of 63 serial studies were 10 hypokalemic patients, 7 patients observed during two or more elevations of serum glycoside and 4 patients briefly described under "additional serial study data patterns" in the Results section. These observations provided an opportunity to correlate serum glycoside pharmacokinetics with cardiac rhythm and serum potassium.

Data collection: Data on each patients history, diagnosis and use of other drugs were obtained from hospital charts. Venous blood samples for glycoside determination were obtained 6 to 24 hours after the last dose of glycoside. In the serial studies, samples were obtained at 24 and 48 hour intervals and before dosing when glycoside continued to be administered. At the time of sampling, blood for determination of blood urea nitrogen and serum electrolytes and 12 lead electrocardiograms or adequate lead II or V_1 rhythm strips were obtained. Data collection continued until both serum glycoside level and cardiac rhythm as assessed from the electrocardiogram, if abnormal, became normal.

The method of serum digoxin radioimmunoassay and its validation in this laboratory were recently described.[15] The iodine-125 kit method has provided a satisfactorily low coefficient of variation in the range of interest. The therapeutic range during this study was considered to be below 2 ng/ml. A lower limit to the therapeutic range was impractical to define because of its dependence on the degree of control contributed by diuretic agents and the dose-response characteristics of the glycosides in individual patients. Serum digitoxin determinations were also carried out by radioimmunoassay utilizing a commercially available kit (Schwarz/Mann, Division of Becton-Dickinson). The upper limit of the therapeutic range was considered to be 30 ng/ml.[3] All serum de-

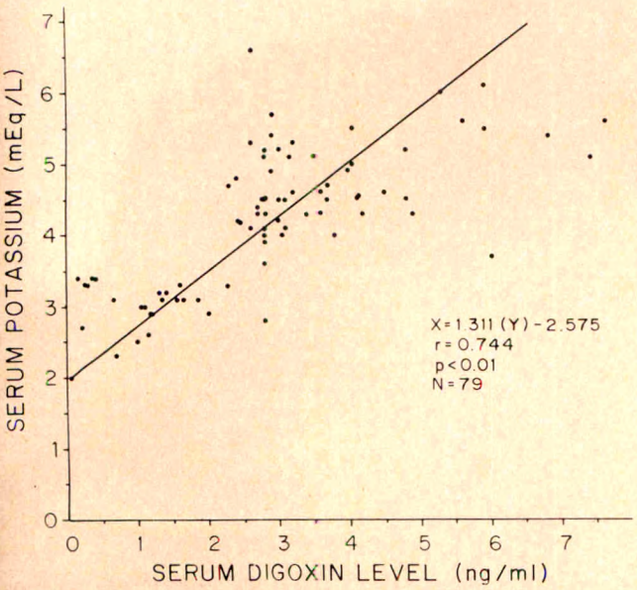


FIGURE 1. Correlation of serum potassium and serum digoxin levels from 79 studies in 73 patients presenting with arrhythmias associated with digitalis intoxication. The *r* value was significant ($P < 0.01$). These data are consistent with a relation between these two factors affecting myocardial sensitivity to arrhythmia induction. L = liter; N = number; p = probability.

terminations were carried out in duplicate, and calibration curves were determined for each batch of serum samples analyzed on a given day.

Results

Digitalized patients presenting with arrhythmias typical of digitalis intoxication: The 79 studies in the 73 patients presenting with qualifying arrhythmias who had been taking prescribed maintenance doses of digoxin yielded two subsets of patients, 55 normokalemic patients and 24 hypokalemic patients (Table I). The difference in mean serum digoxin levels between these subsets was significant ($P < 0.001$). All patients in the normokalemic group had serum digoxin levels over 2 ng/ml, whereas the mean level of the hypokalemic patients was 1.13 ± 0.14 ng/ml (mean ± standard error of the mean). Of the five distinct arrhythmias present in these patients, slow atrial fibrillation and junctional rhythm were absent in the hypokalemic group. There were no statistically significant differences in age or blood urea nitrogen.

TABLE II

Initial Data From 10 Hypokalemic Patients Ranked According to Increasing Serum Digoxin Level

Patient (no.)	Age (yr)	BUN (mg/100 ml)	Serum Potassium (mEq/liter)	SDL (mg/ml)	Arrhythmias
1	57	13	2.7	0.2	+
2	66	19	2.5	1.0	+
3	47	7	2.9	1.2	+
4	63	37	3.1	1.3	+
5	78	52	2.8	1.8	−
6	76	14	2.8	2.8	+
7	53	48	3.3	3.1	−
8	57	35	2.9	3.2	−
9	89	126	3.4	5.4	−
10	61	129	3.4	6.0	+

+ = present; − = absent; BUN = blood urea nitrogen; SDL = serum digoxin level.

The correlation between serum potassium and serum digoxin levels in these 79 patients (Fig. 1) indicated an *r* value of 0.74 ($P < 0.01$). Only 3 of the 24 hypokalemic patients had serum levels of 2 or more ng/ml (2.0, 2.3 and 2.8 ng/ml, respectively). Twenty-one of the 24 hypokalemic patients with arrhythmias (88 percent) had serum digoxin levels below 2 ng/ml, and 6 (25 percent) had levels below 0.5 ng/ml.

Serial studies in 10 hypokalemic patients: Ten hypokalemic patients were selected for study because they were suspected of having digitalis intoxication (Table II). Four of the six patients with arrhythmias had serum digoxin levels below 2 ng/ml. The four patients without arrhythmias had serum potassium levels ranging from 2.8 to 3.4 mEq/liter, with serum digoxin levels ranging from 1.8 to 5.4 ng/ml.

Table III presents the serum digoxin and potassium values before and after potassium administration in the six patients with arrhythmias. In Patient 1 on two occasions, as well as in Patients 2 and 3, there were no

TABLE III

Data During and Immediately After Arrhythmia in Six Hypokalemic Patients

Case (no.)	During Arrhythmia: Serum Potassium (mEq/liter)	During Arrhythmia: SDL (ng/ml)	During Arrhythmia: Other Symptoms	Days Between Observations	After Arrhythmia: Serum Potassium (mEq/liter)	After Arrhythmia: SDL (ng/ml)	Digoxin Therapy
1A*	2.7	0.2	. . .	1	3.9	0.2	Discontinued
1B*	3.3	0.3	. . .	2	3.9	0.3	Discontinued
2	2.5	1.0	Nausea	2	4.3	1.2	Continued†
3	2.9	1.2	. . .	0.5	4.6	0.8	Continued
4	3.1	1.3	. . .	2	‡	. . .	Continued
6	2.8	2.8	Chest pain	3	3.5	1.2	Continued 1 day
10	3.4–3.1	6.0–4.0	Nausea, vomiting	2	3.6	3.3	Discontinued

* Studied on two occasions during hospitalization.
† Temporary pacemaker used with benefit.
‡ Arrhythmia persisted after normal level of serum potassium achieved.
SDL = serum digoxin level.

TABLE IV

Comparison of Data From Normokalemic Patients With Initially Elevated Serum Glycoside Levels Studied Serially and Classified According to Presence or Absence of Arrhythmias Disappearing After Withdrawal of Glycoside and Within 24 Hours of Return of Serum Glycoside Level to Therapeutic Range

	Arrhythmias	No Arrhythmias	*P*
Patients (no.)	17	28	. . .
Age (yr)	62.2 ± 3.1	59.5 ± 2.2	NS
Blood urea nitrogen (mg/100 ml)	33.4 ± 6.7	33.6 ± 5.1	NS
Serum potassium (mEq/liter)	4.7 ± 0.14	4.6 ± 0.15	NS
Serum digoxin (ng/ml) (no. = 14)	4.2 ± 0.33 (no. = 26)	3.6 ± 0.16	= 0.05
Serum digitoxin (ng/ml) (no. = 3)	60.3 ± 10.1 (no. = 2)	75 ± 5.0	. . .
Time to normal digoxin level (days)	4.1 ± 0.5	2.1 ± 0.3	<0.01
Time to normal digitoxin level (days)	7	. . .	
Atrial fibrillation (%)	41	36	. . .
Deaths (%)	29	10.7	NS

NS = not significant; *P* = probability.

substantial differences in the serum digoxin level before and after potassium repletion and return of normal sinus rhythm. In Patient 4 repletion of potassium did not result in disappearance of the arrhythmia. In Patients 6 and 10 there were decreases in serum digoxin levels from 2.8 to 1.2 and 4.6 to 3.3 ng/ml, respectively, associated with repletion of potassium and disappearance of arrhythmia. Thus, in four of seven digitalized hypokalemic patients (57 percent) observed before and after potassium therapy, the serum digoxin levels were within (or below) the therapeutic range during the arrhythmia and were not materially altered at the time of onset of normal sinus rhythm.

Serial observations in 45 consecutive normokalemic patients with high serum glycoside levels: Forty-five normokalemic patients were classified according to presence or absence of arrhythmia (Table IV). Fourteen of the 17 patients with arrhythmias and 26 of the 28 without arrhythmias had been taking digoxin, whereas 3 patients with and 2 without arrhythmias had taken digitoxin. The mean serum digoxin level was higher and the time required for return to less than 2 ng/ml was significantly longer in the group with arrhythmias. There were no material differences in the blood urea nitrogen, serum potassium level or incidence of atrial fibrillation between the two subsets. However, the incidence rate of hospital deaths was nearly three times higher in the arrhythmia group (29 versus 10.7 percent) but was not significant by chi square analysis. In four additional normokalemic patients, similar arrhythmias persisted for more than 24 hours after serum glycoside level returned to the therapeutic range (Table V). In the three patients who had been taking digoxin, arrhythmias persisted for 2 to 11 days, and in the lone patient taking digitoxin, arrhythmias persisted for 6 days after the glycoside level returned to the therapeutic range. The time from presentation to return of serum digoxin levels to 2 ng/ml or less in this subset was a mean of 1 day, and for the patient taking digitoxin, 6 days. Although it was not possible to differentiate these as self-perpetuating rhythms of digitalis intoxication or as coincidental arrhythmias, persistence of arrhythmia for more than 24 hours after the return of serum glycoside level to within the therapeutic range occurred in about 19 percent of the total of normokalemic patients with a high glycoside level and arrhythmias studied in this fashion.

Additional serial study data patterns: Two patients, one with an initial serum digitoxin level of 144 ng/ml and the second with a serum digoxin level of 4 ng/ml, demonstrated disappearance of a qualifying arrhythmia before the return of the glycoside level to the therapeutic range. Two normokalemic patients with a long-term implanted pacemaker had a serum digoxin level of 2.8 and 3.9 ng/ml, respectively. They did not have arrhythmias during the period of elevated serum

TABLE V

Data From Four Normokalemic Patients Whose Arrhythmias Persisted for Over 24 Hours After Serum Glycoside Level Returned to Therapeutic Range

Case (no.)	Drug	Age (yr)	BUN (mg/100 ml)	Serum Potassium (mEq/liter)	SDL (mg/ml)	Time to Normal SDL (days)	Days Arrhythmia Persisted
1	Digoxin	64	23	4.3	2.8	1	11
2	Digoxin	78	27	3.9	2.8	1	2
3	Digoxin	78	72	5.3	2.2	1	5
4	Digitoxin	76	28	5.0	58	6	6
Mean		74	37.5	4.6	2.6*	1*	6*

* Patients receiving digoxin.
BUN = blood urea nitrogen; SDL = serum digoxin level.

TABLE VI

Data From 16 Discrete Episodes of Serum Digoxin Level Elevations (greater than 2 ng/ml) in Seven Patients

Case (no.)	Cardiac Rhythm	Arrhythmia Present: Serum Potassium Level (mEq/liter)	Arrhythmia Present: SDL (mg/ml)	Arrhythmia Absent: Serum Potassium Level (mEq/liter)	Arrhythmia Absent: SDL (mg/ml)
1	AF	4.4	4.2*	4.4	5.2
2	ST	3.6	2.8†	4.7	2.3
3	AF	4.5	3.9‡	. . .	5.0
				4.0	5.0
4	ST	. . .	. . .	5.1	2.6
				. . .	3.9
				. . .	2.7
5	ST	. . .	. . .	2.9	3.2§
				. . .	3.1
6	ST	. . .	. . .	4.8	3.2
				5.5	4.4
7	AF	. . .	. . .	. . .	4.6
				6.1	5.9
Mean	. . .	4.17	3.63	4.69	3.93

* Atrial fibrillation at 46/min.
† Sinus tachycardia with 2:1 atrioventricular block after carotid massage.
‡ Atrial fibrillation at 40/min with 3 second pauses.
§ High serum digoxin level and hypokalemia.
AF = atrial fibrillation; SDL = serum digoxin level; ST = sinus tachycardia.

digoxin levels. Data from these four patients are not shown.

Incidence of arrhythmias in patients who had elevated serum digoxin levels on two or more occasions: Seven patients were observed during two or three (two patients) discrete elevations of serum digoxin level separated by periods during which serum levels were close to or below 2 ng/ml (Table VI). Five patients had ischemic heart disease, one rheumatic heart disease (observed before and after mitral commissurotomy) and one chronic obstructive pulmonary disease. Their ages ranged from 55 to 74 years (mean 59.3). The intervals between elevated levels ranged from 36 hours to 30 days. Three patients had atrial fibrillation and four sinus rhythm. Occasional supraventricular or ventricular premature contractions were common in this group, but the criteria for diagnosis of arrhythmia due to digitalis intoxication were applied as described under Methods. There were 16 serum digoxin level elevations, only 3 of which were associated with a qualifying arrhythmia. Four patients, three with sinus tachycardia and one with atrial fibrillation, never manifested arrhythmia (nine episodes of high digoxin level). Of the three patients with arrhythmias, two exhibited an arrhythmia on one of two occasions, and the third patient on one of three occasions of high digoxin levels. Two of these three had atrial fibrillation. There appeared to be no correlation between serum digoxin or serum potassium level and occurrence of arrhythmia, nor was a sequential pattern of occurrence evident (Table VI).

Arrhythmias were present during only 3 of these 16 episodes (19 percent) of serum level elevation in these seven patients. Other symptoms, such as nausea and vomiting, were rare. One patient died in the hospital (subset mortality rate 14 percent).

Discussion

We believe that these observations demonstrate the considerable inter- and intraindividual variations in serum glycoside concentrations at which digitalis-induced arrhythmias may develop in a representative group of patients with heart disease. Clinicians had suspected such variations from bedside observations,[11] and differences in inotropic response and toxic threshold between two small groups of patients with cardiomyopathy were recently documented.[12] These and other available data lend support to the contention that no arbitrary serum glycoside value will independently diagnose digitalis toxicity with sensitivity.[10,16] This contention is also consonant with prior studies of serial deliberate digitalis intoxication, carried out before the availability of serum measurements, which demonstrated the unpredictability of arrhythmia induction.[17] However, serum glycoside levels can provide valuable data for monitoring pharmacokinetics in vivo and for optimizing treatment regimens.[4,9]

Serum digoxin and potassium levels and relation to arrhythmias: The poor absolute relation of serum digoxin level to arrhythmias was clearly evident in the hypokalemic and normokalemic patients. Although these results might have been predicted from previous studies of digitalis-associated arrhythmias in hypokalemic states,[18,19] they provide extensive proof of a large incidence of arrhythmias in patients with normal serum digoxin levels and hypokalemia. The potassium repletion experiments suggest at least a frequent determining role of the serum potassium level or the intracell/extracell potassium ion ratio, or both, in the development of myocardial arrhythmias at constant low serum digoxin levels. The significant correlation between serum potassium and digoxin level in patients

with arrhythmias may be taken to approximate an arrhythmia threshold through a spectrum of clinically encountered concentrations of serum potassium and digoxin.

Explanation for noncorrespondence between serum glycoside levels and arrhythmia: Altered or variable myocardial threshold for induction of arrhythmias by digitalis seems to best explain the observations of noncorrespondence between serum glycoside levels and arrhythmias reported in a variety of circumstances. These observations include "overlap" of values in toxic and nontoxic patients[2]; production of toxicity by induced hypokalemia at constant therapeutic digitalis levels[20,21] (and present study), or disappearance of arrhythmias with repletion of potassium at constant digitalis levels (present study); poor correspondence between serum digoxin levels and sensitivity to infusions of acetylstrophanthidin[5,12]; variable rate response to any given glycoside level in groups of patients with atrial fibrillation,[22] or variable response of a given patient to elevations of serum glycoside levels (present study) or to large doses of glycosides.[18] There are no data to indicate that all normal persons or those with cardiac disease should be expected to manifest arrhythmias at any specific serum glycoside concentration. Clearly, neonates have a generally increased resistance to the glycosides that tends to subside with age.[23,24] Similarly, the normal adult heart not only is more resistant than the abnormal heart to digitalis poisoning,[25] but also, when such poisoning occurs, tends to exhibit different rhythms from those of the diseased heart. Analysis of the signs and symptoms observed in an epidemic of digitoxin-digoxin intoxication in patients with heart disease revealed frequent resistance to the development of arrhythmias,[26] as shown by our data on patients who had multiple elevations of glycoside levels. An epidemiologic study demonstrating an association between increased use of kaliuretic diuretic drugs and increased frequency of digitalis intoxication[27] agreed with our short-term data and those of Steiness and Olesen[20] that, under otherwise constant clinical conditions, potassium deficiency may be a key determinant of susceptibility to arrhythmia induction. Finally, a retrospective review[4] of a prospective study of digitalis intoxication indicated that arrhythmias at so-called therapeutic glycoside levels tended to occur in patients who had the most severe chronic heart disease and were therefore considered "sensitive."

Defining a serum glycoside level to distinguish toxicity: Inasmuch as digitalis toxicity, whether defined by electrocardiographic criteria or by symptoms, appears to be related to complex incompletely described factors, the threshold for glycoside toxicity, however defined, will apparently show significant variation within any given patient and from patient to patient. Consideration of our data and those of others from both normal and abnormal hearts indicates that serum values as low as 0.2 ng/ml to perhaps as high as 9 ng/ml (observed in a suicidal ingestion in this institution) may be associated with arrhythmias. Thus, because all of the heart diseases in which glycosides are used form a spectrum or continuum of severity, and at each point on the continuum multiple factors play on the susceptibility of myocardial tissue to arrhythmias, it would be difficult to define any arbitrary clinically useful glycoside level that would accurately distinguish toxicity.

Sensitivity and predictive accuracy of a high serum glycoside level: Our data on the consecutive normokalemic patients with high serum glycoside levels, as well as other representative studies,[25,28,29] support the general observation that digitalis intoxication is statistically more likely in normokalemic digitalized patients with serum glycoside levels above 2 ng/ml. Nevertheless, Butler and Lindenbaum's groupings[9] of patients into resistant or sensitive categories seems useful because in patients with hypokalemia,[21] amyloid heart disease[12] or acute myocardial infarction,[30,31] the mean glycoside level associated with digitalis-induced arrhythmias may well be less than 2 ng/ml, within the so-called therapeutic range. The specificity and predictive accuracy of a high serum level for a qualifying arrhythmia in our nearly consecutive series of normokalemic patients with a high serum glycoside level was 62 percent (specificity rate) and 38 percent (rate of predictive accuracy). The sensitivity rate of elevated levels in the mixed hypo- and normokalemic group presenting with arrhythmias was 72 percent. A problem in using the proposed formulation of Ingelfinger and Goldman[10] for a more precise testing of the independent value of the serum concentration is that almost *any patient taking digitalis* who has acceptable signs or symptoms, or both, of toxicity would (should) be presumed by most clinicians to have toxicity irrespective of the serum digoxin level. Small subsets of digitalized patients might be judged to have these signs or symptoms for reasons other than digitalis toxicity, but in our experience these are extremely complex clinical cases in which definitive judgment concerning the etiology of the arrhythmia is virtually impossible because of coexisting myocardial infarction, pneumonia, shock, hypokalemia and the presence of glycosides.

Myocardial intotropic effect and toxicity: Despite the difficulties in the diagnosis of digitalis intoxication, several studies of the myocardial response after acute digitalization[13,32,33] and after chronic alterations in dose and serum level[34,35] have demonstrated a good relation between the dose or serum level of digitalis, or both, and its inotropic effect. In model experiments in which increased potassium was provided (preventing development of arrhythmias), increasing inotropy was noted with increasing doses of glycoside productive of toxicity in unprotected animals.[32] This finding contrasts with the inconsistencies between serum levels and chronotropic effects in patients with atrial fibrillation,[22] although some studies do indicate a rough correspondence between serum levels and resting and exercise heart rates.[36,37] Correlations of myocardial effects with serum levels can be helpful in assessing the adequacy of digitalization in many patients.[4,9,33,34]

Modern drug regimens combining potent diuretic

drugs with digitalis may be responsible for blurring the relation between the serum glycoside concentration and the myocardial response or cardiac manifestations of toxicity, or both. Doherty[38] advocated administering less than maximal tolerated glycoside in combination with other suitable drugs in order to reduce the incidence of toxic rhythms and their associated high mortality rate. This practice would result in generally lower serum digitalis concentrations, whereas antiarrhythmic agents or potassium supplements, or both, may act to raise the tolerated digitalis serum concentration.[32]

Serum level versus myocardial tissue concentration: The linear relation of the serum/myocardial tissue ratio of concentrations has been well established in the steady state after average digitalizing or maintenance doses.[39] This observation led to the important concept that under ordinary clinical conditions, the serum level would be related to the myocardial digoxin concentration and, presumably, the myocardial response. These relations may be unclear in the presence of other drugs, as indicated earlier. Further, there may be reason to doubt the linearity of serum/tissue concentration ratios at high levels of glycoside and, particularly, in the unsteady states accompanying onset and offset of toxicity.[40] In an acute whole dog study, Marcus[21] showed hypokalemia to alter myocardial digoxin uptake, and we[42] showed altered serum:myocardial concentration ratios to be present in intoxicated, normokalemic dogs. The few studies of disappearance times in patients poisoned with digoxin appear to show altered pharmacokinetics.[40] If periods of nonlinearity between serum and myocardial concentrations occur, as seems likely in these clinically relevant models, another series of unpredictable, albeit temporary, problems in relating serum digoxin levels to signs or symptoms of intoxication would be present.

Clinical implications: Serum glycoside level determinations are an important tool for investigation and for patient management.[28,42] Their value and limitations[6,10] should be understood by all physicians who utilize them. Our present view is that the serum glycoside level has sharp limitations as an independent diagnostic indicator of toxicity but that it can be used, with the appropriate correlative facts, as an accurate mirror of myocardial threshold to arrhythmias associated with glycoside toxicity and in regulating the management of digitalized patients.

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Fascicular Conduction Disturbances After Coronary Bypass Surgery

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Two hundred patients undergoing coronary bypass graft surgery were studied to determine the frequency and significance of new fascicular conduction disturbances. The follow-up period ranged from 13 to 39 months. New disturbances developed in 39 patients (20 percent). Isolated right bundle branch block (6 percent) and left anterior hemiblock (6 percent) were the most common disturbances. Right bundle branch block was usually transient and was not associated with further complications in the follow-up period. However, patients with either transient or persistent left bundle branch block or left anterior hemiblock, or both, had (1) increased late mortality compared with patients without new fascicular conduction disturbances (5 of 26 versus 11 of 161; $P < 0.02$), and (2) increased late myocardial infarction (2 of 26 versus 2 of 161; $P < 0.05$). New left fascicular conduction disturbances after coronary surgery identified a subset of patients with more extensive ischemic heart disease, suggesting that these patients require close follow-up care.

With wide acceptance of bypass grafting for treatment of coronary artery disease, the risks and benefits of the procedure need to be clarified. Many studies have dealt with relief of symptoms,[1–3] perioperative infarction[4–7] and early or late mortality.[8–10] Little attention has been given to the occurrence of electrocardiographic changes without infarction and the development of perioperative fascicular conduction disturbances.

We report in this study the incidence and clinical significance of fascicular and bundle branch conduction disturbances that may complicate coronary bypass surgery. We have observed that fascicular conduction disorders are often transient, and patients who manifest either left bundle branch block or left anterior hemiblock, or both (in contrast to right bundle branch block) may be at increased risk for mortality and morbidity in the late postoperative period.

Methods

Patients: Two hundred patients were selected at random from 400 consecutive patients undergoing only coronary bypass surgery without concomitant valve replacement or aneurysmectomy from November 1973 to February 1975. There was an approximately equal number of patients selected from the periods when total body hypothermia and selective cardiac hypothermia were used as a means of myocardial preservation. All patients undergoing coronary bypass grafting were included in the study regardless of the indications for surgery or the presence of preexisting cardiac or noncardiac disease.

Surgical technique: All operations were performed by one of us (H.M.). The operation was conducted through a mid sternal incision. The edges of the pericardium were sutured to the sternal edge to form a pericardial basket. Patients were given heparin (300 units/kg body weight) before cannulation with one or two venous return catheters through the right atrium. A no. 24 flexible aortic arch catheter was inserted into the ascending aorta for arterial perfusion. Immediately after cannulation, sufficient blood was removed to reduce the he-

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matocrit to 25 percent. This blood was stored in bags containing acid citrate dextrose solution to be reinfused at completion of surgery. A Travenol Variflow bubble oxygenator was primed with 2,000 cc of electrolyte solution and 1,000 cc of plasma. Bypass was instituted at 2.2 liters/min per m^2 and then increased to a nomogram-predicted value to maintain a mean aortic pressure of more than 50 mm Hg with a Sarns model 2000 pump.

The myocardium was preserved either with total body hypothermia, which reduced the basal temperature to 32° C, or with selective cardiac hypothermia, which resulted in perfusion of the coronary arteries with cold blood at 15° C. A 4 to 5 mm circular hole was cut in the root of the aorta, which was then clamped. A no. 12 mushroom-tip catheter was connected to an arteriotomy suction source and inserted into the hole in the aorta to decompress the aortic root and the left side of the heart. Periods of ischemic arrest were limited to 12 to 21 minutes by intermittent release of the aortic cross-clamp. After insertion of the proximal and distal anastomoses, the heart was electrically defibrillated, and prophylactic atrial and ventricular pacing wires were inserted.

During the procedure, blood electrolytes, pH, PO_2 and PCO_2 were frequently monitored and potassium chloride was given as needed to maintain a normal serum potassium level. A standard 12 lead electrocardiogram was obtained within 1 hour after operation and at least once daily thereafter. Standard cardiac medications were given when clinically indicated in the postoperative period.

Data collected: The following data were coded and stored in the University of Pennsylvania computer data bank: the patient's age, sex and history of hypertension, cigarette smoking or hyperlipidemia; preoperative administration of digitalis or propranolol; occlusion of coronary vessels (at least 50 percent reduction in luminal diameter); previous myocardial infarction or fascicular conduction disturbance; bypass time; aortic cross-clamp time; type of myocardial preservation (total body or selective cardiac hypothermia); hematocrit after operation; initial recovery room temperature, pH or electrolyte abnormality in the operative or perioperative period, and evidence of new myocardial infarction or fascicular conduction disturbance in the postoperative electrocardiogram. New myocardial infarction was defined as the development of permanent pathologic Q waves not present before operation (New York Heart Association criteria[11]). Changes in serum enzymes were not evaluated in this study, and radionuclide imaging was not performed.

Fascicular disturbances: Follow-up data were obtained 13 to 39 months after discharge in all cases and included the presence of recurrent angina, myocardial infarction or death. The fascicular conduction disturbances recorded were right bundle branch block, left anterior hemiblock, left bundle branch block and combined right bundle branch block with

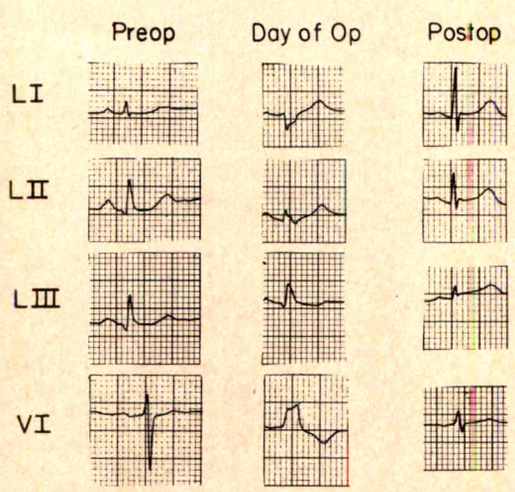


FIGURE 1. Electrocardiographic sequence demonstrating the development on the day of operation (Op) of new right bundle branch block not evident in the preoperative (Preop) electrocardiogram and its disappearance in the early postoperative (Postop) period.

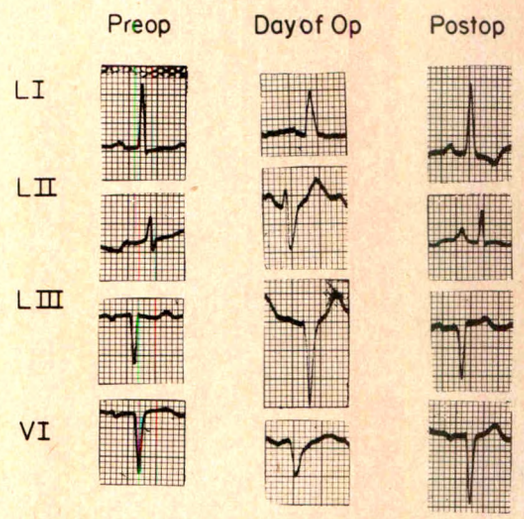


FIGURE 2. Electrocardiographic sequence demonstrating the development of new left anterior hemiblock on the day of operation (Op) that was not evident in the preoperative (Preop) electrocardiogram and its disappearance in the early postoperative (Postop) period.

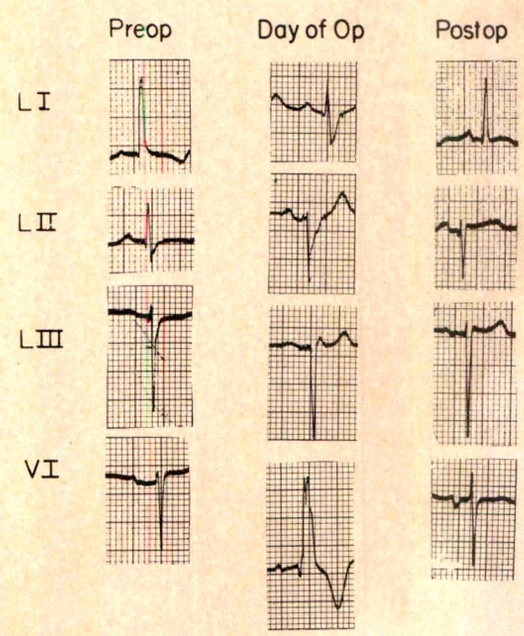


FIGURE 3. Electrocardiographic sequence demonstrating the development of new right bundle branch block with left anterior hemiblock on the day of operation (Op) that was not evident in the preoperative (Preop) electrocardiogram. Left anterior hemiblock persisted after the disappearance of right bundle branch block in the early postoperative (Postop) period.

TABLE I

Summary of Cases

	New Fascicular Conduction Disturbances and Complete Heart Block	No New Fascicular Conduction Disturbances	*P* Value
Number of patients	39	161	NS
Age (yr)	55 ± 7.4*	52 ± 8.4*	NS
Male patients (no.)	31 (79)	129 (80)	NS
Hypertensive	14 (33)	56 (35)	NS
Smokers	24 (60)	103 (64)	NS
Hyperlipidemia	9 (23)	61 (38)	NS
Preoperative use of digitalis	8 (20)	18 (11)	<0.05
Preoperative use of propranolol	17 (43)	85 (53)	NS
Coronary artery disease			
Left main +	2 (5)	8 (5)	NS
1 vessel	6 (15)	26 (16)	NS
2 vessel	9 (23)	52 (32)	NS
3 vessel	24 (62)	83 (52)	NS
Previous MI			
Anterior	6 (15)	21 (13)	NS
Inferior	7 (18)	27 (17)	NS
Perioperative MI	7 (18)	21 (13)	NS
Previous FCD	2 (5)	11 (7)	NS
Bypass time (min)	101 ± 23*	97 ± 83*	NS
Aortic cross-clamp time (min)	35 ± 13*	31 ± 22*	NS
Hypothermia			
Total body	21 (55)	80 (48)	NS
Selective cardiac	18 (48)	81 (52)	NS
Hematocrit in SICU	27 ± 4*	26 ± 5*	NS
Initial SICU temperature	98.1 ± 2.5*	98.1 ± 2.2*	NS
Abnormal serum K^+ in SICU	12 (30)	50 (31)	NS
Abnormal pH in SICU	16 (40)	75 (47)	NS
Recurrent angina	2 (5)	2 (3)	NS
Recurrent MI	2 (5)	2 (1)	NS
Death in follow-up period	5 (13)	11 (7)	NS

* Mean ± standard deviation.
Values in parentheses indicate percent of cases.
FCD = fascicular conduction defect; MI = myocardial infarction; NS = not significant; *P* = probability; SICU = surgical intensive care unit.

left anterior hemiblock. Diagnosis was based on criteria of the New York Heart Association.[11]

The clinical perioperative and surgical variables were then correlated with the presence or absence of new fascicular conduction disturbances. Means and standard deviations were used for quantitative data, and groups were compared with use of Student's *t* test, chi square analysis or Fisher's exact test.

Results

Patient data: The mean age of the 200 patients was 52.8 ± 8.4 years. There were 40 women (20%) and 160 men (80%). Sixty-one patients (31 percent) had a preoperative myocardial infarction (anterior in 27 [14 percent] and inferior in 34 [17 percent]). Thirteen patients (6 percent) had previous fascicular conduction disturbances: right bundle branch block (two patients), left bundle branch block (one patient), left anterior hemiblock (eight patients) and right bundle branch block with left anterior hemiblock (two patients). Two of the 13 had additional fascicular conduction disturbances after coronary surgery. One patient with previous left anterior hemiblock and one with right bundle branch block each had transient postoperative left bundle branch block. Before operation 26 of the patients (13 percent) had been given digitalis and 92 (46 percent) propranolol. Angiography revealed disease of the left main coronary artery in 10 patients (5 percent), single vessel disease in 32 patients (16 percent), two vessel disease in 61 patients (31 percent) and three vessel disease in 107 patients (53 percent).

Incidence of new fascicular conduction disturbances: Fascicular conduction disturbances and complete heart block not present before operation developed in 39 of the 200 patients (20 percent) who underwent coronary bypass surgery (Tables I and II; Fig. 1 to 3). Isolated right bundle branch block and isolated left anterior hemiblock each developed in 12 of 200 patients (6 percent). Right bundle branch block with left anterior hemiblock was the next most frequently observed disorder, affecting seven patients (4 percent). Left bundle branch block developed in six patients (3 percent). Complete heart block developed in two patients.

Persistence of fascicular conduction disturbances: Fascicular conduction disturbances that disappeared within 5 days after operation were considered *transient*; those lasting longer were considered *persistent*. In 12 patients, the fascicular conduction disturbances resolved within 24 hours. Left anterior hemiblock was the most frequent persistent fascicular conduction disturbance (8 of 12 patients, 67 percent), and right bundle branch block was most commonly transient, persisting in only 1 of 12 patients (8 percent). Of the seven patients with combined right bundle branch block and left anterior hemiblock, the left anterior hemiblock persisted in four, and the right bundle branch block alone in two. In one patient both blocks disappeared and no patient had persistence of both right bundle branch block and left anterior hemiblock. Among six patients with postoperative left bundle branch block, the block resolved in three (50 percent) and persisted in one; in two, only left anterior hemiblock persisted.

Factors associated with development of fascicular conduction disturbances: Only one significant difference was found between the 39 patients with postoperative fascicular conduction disorders and the 161 patients without such disorders (Table I). Digitalis had been taken preoperatively by 8 of the 39 patients (20 percent) with fascicular conduction disturbances but by only 18 (11 percent) of those without such disturbances ($P < 0.05$). Bypass time and aortic cross-clamp time were greater in those patients with fascicular conduction disturbances, but the differences were not statistically significant.

Only one characteristic had significance in relation to the type of fascicular conduction disturbance that developed. Preoperative myocardial infarction was present in 7 of 12 patients with right bundle branch block but in only 4 of 12 with left anterior hemiblock

TABLE II

Summary of New Fascicular Conduction Disturbances

New Fascicular Conduction Disturbances	no. (%)	Duration (days)	Previous FCD	Previous MI	Periop MI	Abnormal serum K/pH	TBH/SCH	Mean Bypass Time (min)	Mean Aortic Clamp Time (min)	Postop AP/MI	Death
LBBB											
Transient	3 (50)	1.5	1.0	...	...	1/1	2/1	112	44	0/1	1
Persistent	1 (17)	...	...	...	...	0/0	1/0	125	...	...	1
Persistent LAH	2 (28)	...	...	...		0/0	0/2	101	44	...	1
RBBB											
Transient	11 (92)	1.5	...	7	2	4/5	5/6	99	53	2/0	...
Persistent	1 (8)	...	...	...	...	0/1	1/0	60	...	...	...
LAH											
Transient	4 (33)	1.5	...	1	1	2/1	1/3	115	29	...	1
Persistent	8 (66)	...	1.0	3	2	3/5	5/3	101	39	0/1	...
RBBB/LAH											
Transient	1 (14)	1	...	1	...	0/0	0/1	140	...	...	...
Persistent LAH	4 (57)	...	...	1		2/1	3/1	105	18	...	1
Persistent RBBB	2 (28)	...	...	...	...	0/1	2/0	67	...	...	...
Persistent RBBB/LAH	0 (0)	...	...	...	...	...	...	...	...	...	...
Complete heart block											
Transient	1 (50)	1	...	...	...	0/0	1/0	100	...	...	...
Persistent LAH	1 (50)	...	...	...	...	0/1	0/1	89	24	...	...
Total	39	1.2	2	13	7	12/16	21/28	101	35	2/2	5

AP = angina pectoris; FCD = fascicular conduction disturbances; LAH = left anterior hemiblock; LBBB = left bundle branch block; MI = myocardial infarction; RBBB = right bundle branch block; SCH = selective cardiac hypothermia; TBH = total body hypothermia.

and in 2 of 7 with right bundle branch block plus left anterior hemiblock ($P < 0.05$). Perioperative infarction could not be recognized when left bundle branch block developed, but in one of the six patients it was recognized when the left bundle branch block resolved.

Relation of fascicular conduction disturbances to clinical course and prognosis: There were no significant differences among the patients who had recurrent angina (2 of 39 [5 percent of those with new fascicular conduction disturbances] versus 2 of 161 [1 percent of those without new fascicular conduction disturbances]). However, 5 of 26 patients (20 percent) who had new transient or permanent left conduction system delays (left bundle branch block or left anterior hemiblock, or both) died in the follow-up period compared with 11 of 161 patients (7 percent) without new fascicular conduction disturbances ($P < 0.02$). Similarly, the incidence of new myocardial infarction in the follow-up period was greater among patients with new left conduction system defects than among those without new conduction disturbances (2 of 26 [8 percent] versus 2 of 161 [1 percent]; $P < 0.05$).

Discussion

Our findings confirm that fascicular conduction defects may complicate the early postoperative course of patients undergoing coronary bypass graft surgery. They were observed in approximately 20 percent of our study group. Approximately one third of the disturbances were transient, lasting less than 24 hours. Right bundle branch block was most often transient, and left anterior hemiblock was most often persistent. Previous studies[12–14] implied the occurrence of transient fascicular conduction defects after coronary surgery but did not provide a full analysis. Selzer and Cohn[14] reported a potential 5 to 15 percent incidence rate of postoperative fascicular conduction disturbances after coronary surgery, a percent similar to that found in our study. Satinsky et al.[15] found a 5 percent incidence rate. We assessed the incidence of fascicular conduction defects using a routine method of obtaining an initial electrocardiogram within 1 hour after coronary bypass surgery and once daily thereafter. We suspect that the incidence may be greater if more frequent electrocardiograms are taken.

Our data also suggest that either new permanent or transient left fascicular conduction disturbances in the perioperative period identify a high risk group for subsequent new myocardial infarction or sudden death in the next 13 to 39 months. By contrast, the course of patients with new permanent or transient right bundle branch block appears to be benign.

Predisposing factors: The prevalence of preoperative use of digitalis and of preoperative myocardial infarction was significantly greater among patients who had postoperative fascicular conduction defects than among those who did not. There was also a greater aortic cross-clamp time and total extracorporeal bypass time in those with postoperative fascicular conduction defects, but this difference was not statistically significant. The development of fascicular conduction defects was not associated with metabolic factors such as pH or potassium abnormalities or the type of myocardial preservation utilized during surgery. Some workers have

suggested that hypothermia may cause electrocardiographic conduction defects, but our data clearly show that the frequency of perioperative conduction disturbances was not different in those patients undergoing selective cardiac hypothermia versus total body hypothermia during cardiac bypass. In addition, the development of fascicular conduction defects was not associated with the number of coronary bypass grafts performed or the extent of preoperative coronary disease.

Significance of fascicular conduction disturbances: It is likely that transient ischemia in the perioperative period affecting the conduction system is responsible for the fascicular conduction disturbances noted. It is also likely that permanent conduction disturbances represent irreversible ischemic damage to the conduction system whereas transient disturbances may indicate reversible ischemia. Because digitalis therapy is routinely discontinued 24 hours before coronary surgery and because digitalis does not prolong infranodal conduction time,[16] the more frequent preoperative use of digitalis in patients with postoperative fascicular conduction defects merely indicates that these patients had more severe myocardial disease. There was an increased prevalence of preoperative myocardial infarction in patients with postoperative fascicular conduction defects and a trend toward a greater incidence of such defects in patients experiencing greater operative bypass time or aortic cross-clamp time. These findings further suggest that patients with these defects have more extensive myocardial disease and are therefore potentially at increased risk for ischemic events during surgery.

Clinical implications: As mortality rates during coronary bypass surgery have been reduced, more attention has been given to complications of this operation. Our data suggest that new fascicular conduction disturbances in the perioperative period after coronary bypass grafting are not uncommon and that even the transient appearance of left bundle branch block or left anterior hemiblock, or both, appears to be associated with increased morbidity and mortality, probably because patients with such defects have more extensive ischemic heart disease. We therefore suggest that patients with new left fascicular conduction defects warrant close follow-up after coronary bypass surgery.

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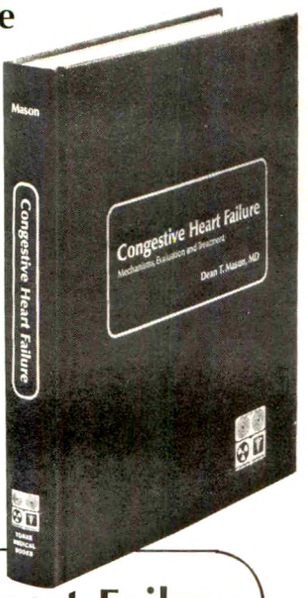
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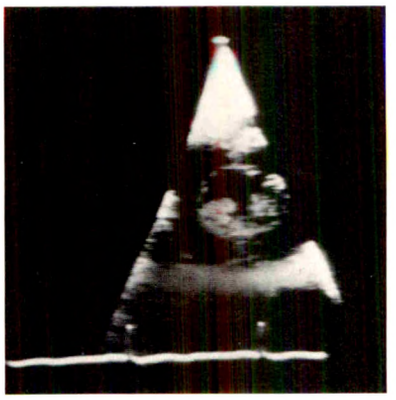
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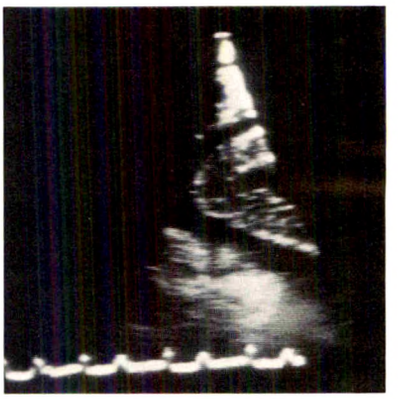
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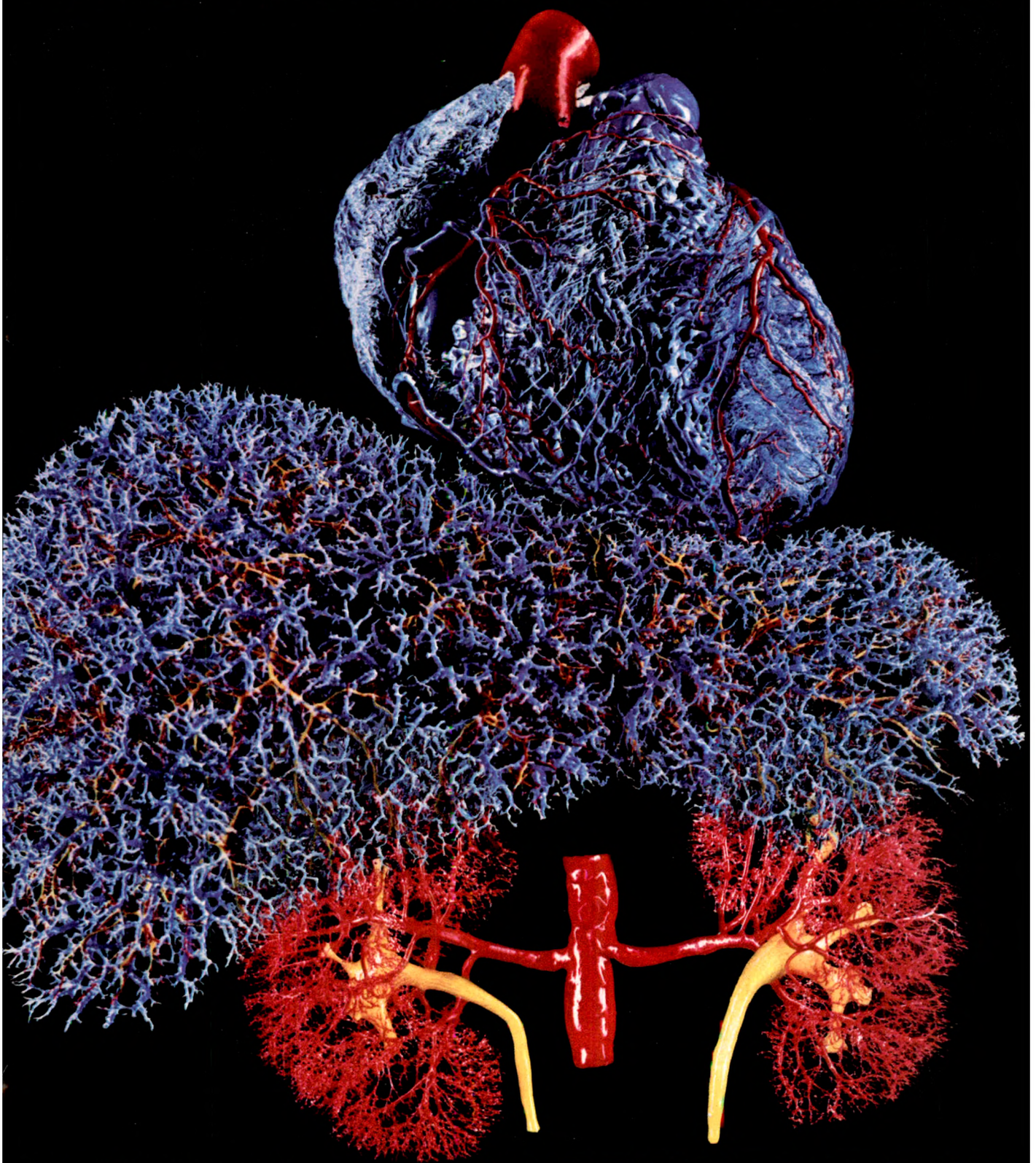
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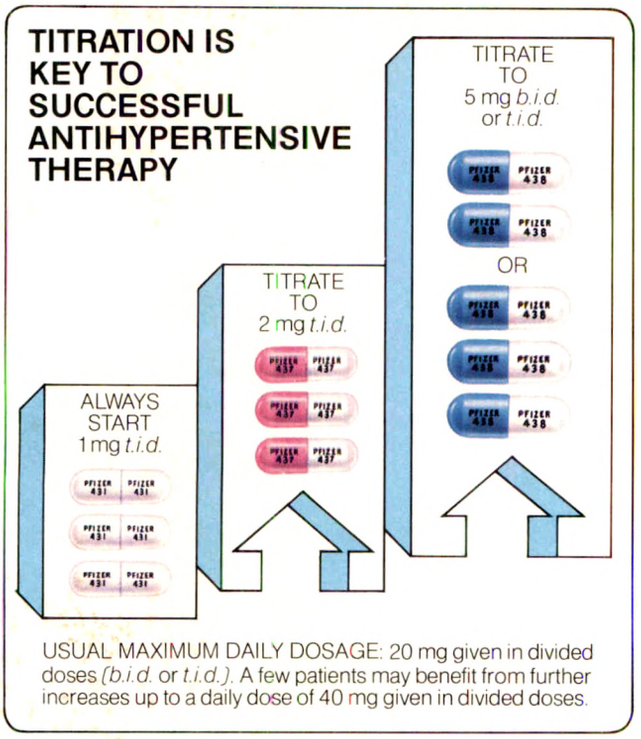


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EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

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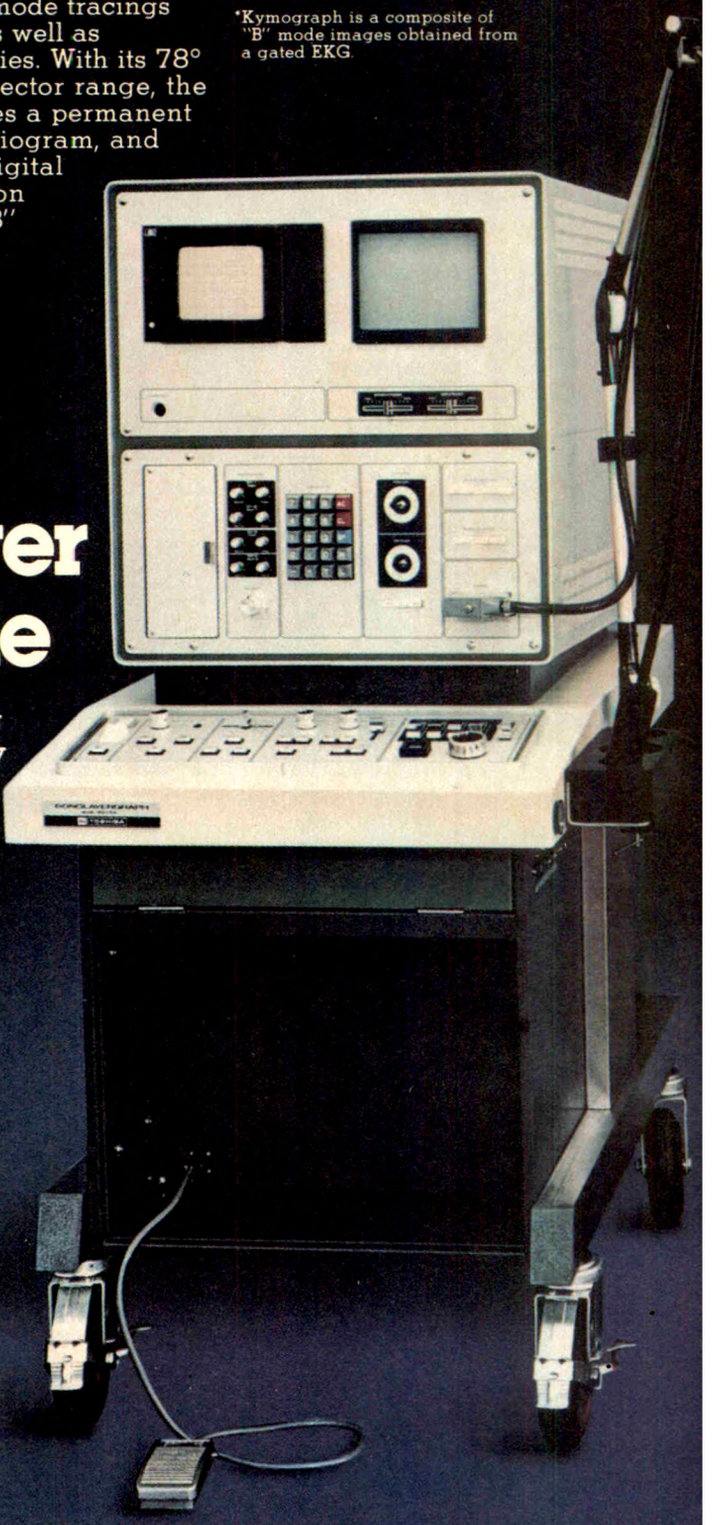
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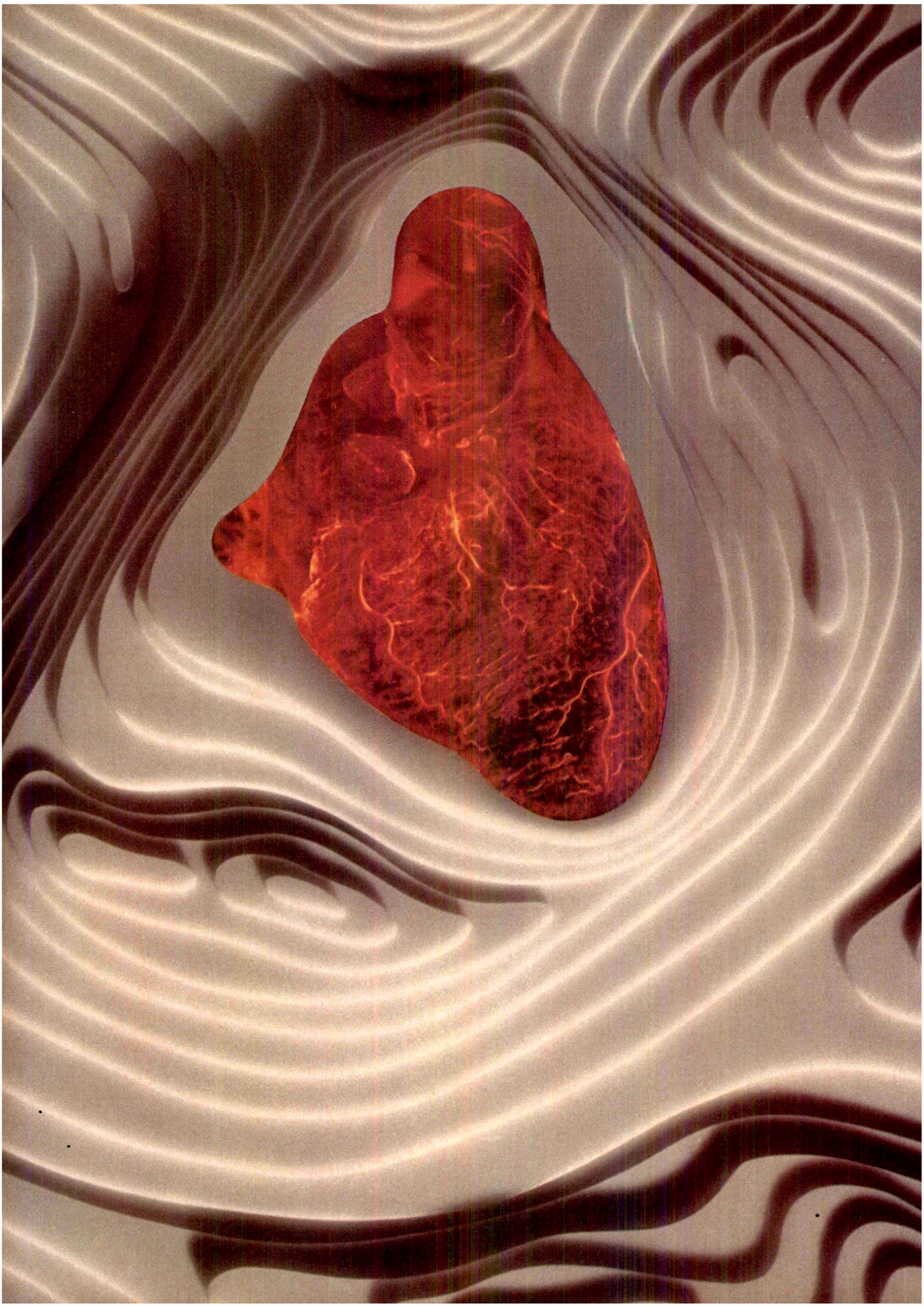
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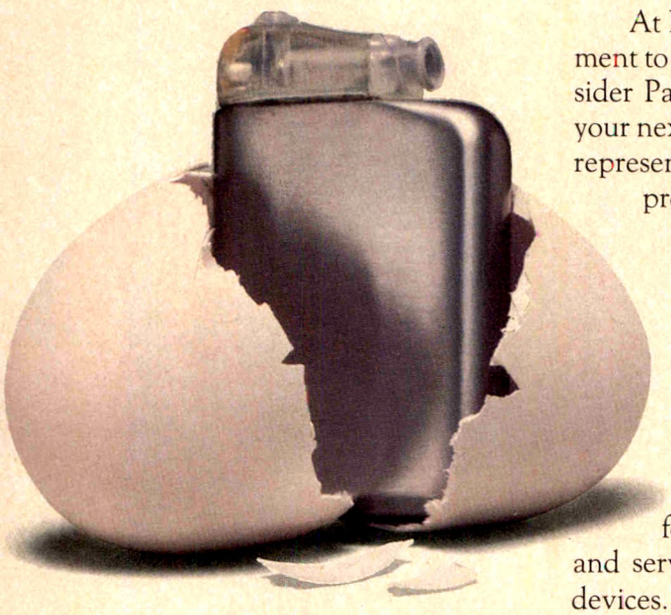
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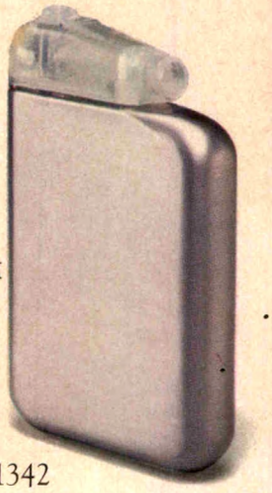
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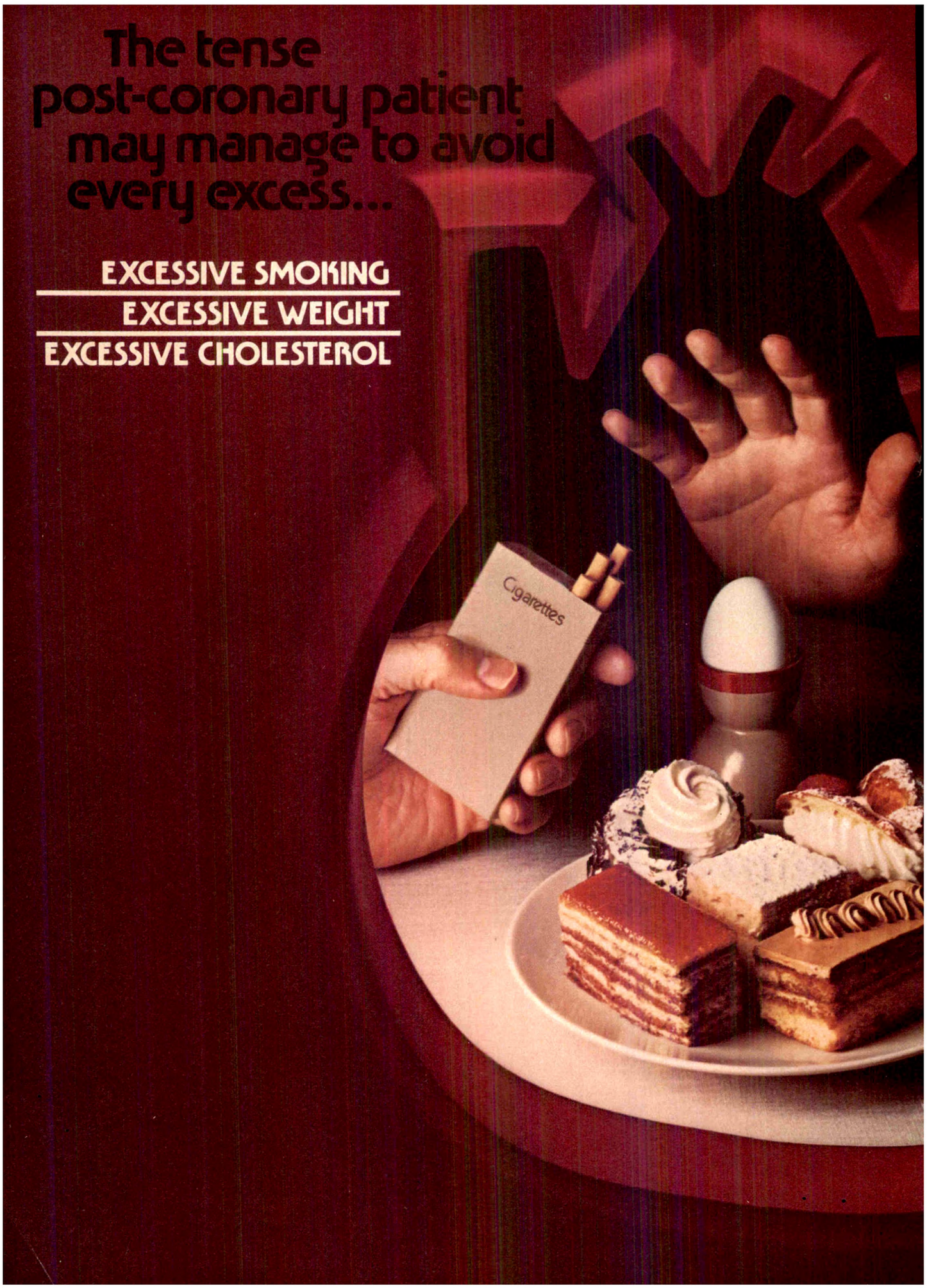
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The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

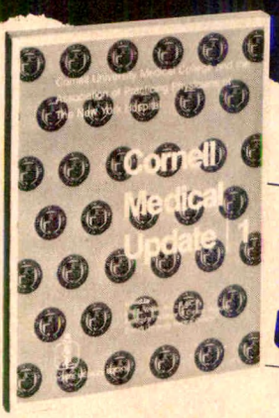
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Hemodynamic Significance of the Length of a Coronary Arterial Narrowing

ROBERT L. FELDMAN, MD*
WILMER W. NICHOLS, PhD
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Gainesville, Florida

The hemodynamic significance of the length of a coronary arterial narrowing is unclear. Accordingly, the influence of the length of a given coronary narrowing on coronary hemodynamic responses was studied in 14 dogs. Recordings were made as short fixed diameter reductions were progressively lengthened to 5, 10 and 15 mm by the addition of plastic occluders. Resting coronary blood flow decreased and pressure gradients developed across short (snare) narrowings greater than 80 percent (critical stenosis). Short 40 to 60 percent narrowings had no significant resting hemodynamic influence, but increasing their length to 10 and 15 mm consistently resulted in significant pressure gradients and flow reductions. Reactive hyperemic coronary blood flow expressed as repayment of flow debt (after 10 seconds of coronary occlusion) decreased progressively as these narrowings were lengthened. The effect of 15 mm long narrowings on resting and reactive hyperemic flows was similar to that of short 90 percent narrowings.

These data indicate that there is uncertainty about the significance of coronary diameter reductions previously considered hemodynamically unimportant. In our studies, significant changes in resting and reactive hyperemic coronary flows and resting pressure gradients occurred as the length of a given degree of narrowing was increased.

A major question concerning the clinical evaluation of patients with coronary artery disease relates to the degree of coronary narrowing that constitutes functionally significant obstruction. Although luminal size must be substantially decreased before a pressure gradient or reduction in blood flow is detected,[1–3] there is no general agreement on the precise degree of narrowing considered significant. The American Heart Association Committee Report[4] accepts an 80 percent reduction of vessel diameter as significant on the basis of studies demonstrating increased resting pressure gradients at operation only across narrowings of at least this magnitude.[5] However, many investigators[6–9] consider that a 50 percent reduction of vessel diameter is capable of producing ischemia and is a useful clinical and prognostic measure. Insight into this disparity is provided by animal experiments demonstrating that short 50 percent narrowings produce no hemodynamic change at low flow rates but may result in impairment of flow at higher flow rates.[1] In light of the foregoing, current evaluation of a coronary arterial narrowing focuses on estimation of reduction of vessel diameter. The possible hemodynamic importance of the length of a given obstruction is generally disregarded.

Accordingly, we evaluated the coronary hemodynamic effects of the length of a coronary arterial narrowing in an animal model. Diameter reductions of 40 to 60 percent were used because short narrowings of this degree do not alter coronary flow at low flow rates.[1,2] Coronary flow and changes in pressure gradient between the aorta and distal coronary artery

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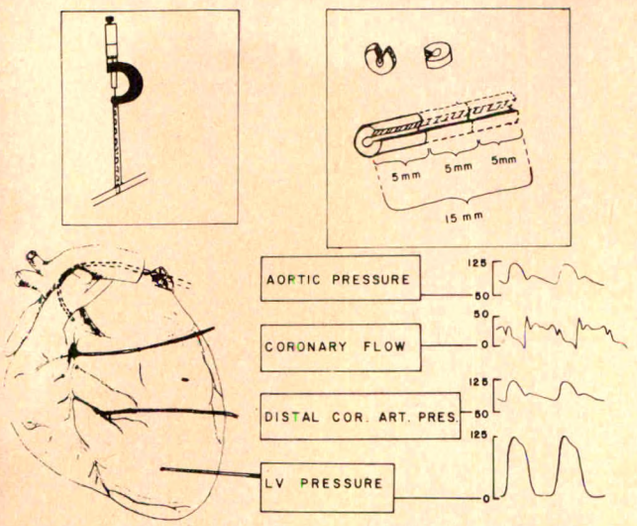


FIGURE 1. Diagram of experimental model with appropriately placed distal coronary arterial and ascending aortic pressure catheters and representative tracings. Coronary flow is measured from a proximally positioned flow transducer. The **top left** inset shows the modified machinist micromanometer snare allowing calibrated reduction in vessel circumference. The **top right** panel shows a set of occluders used to produce narrowings of increasing length. COR. ART. PRES. = coronary arterial pressure; LV = left ventricle.

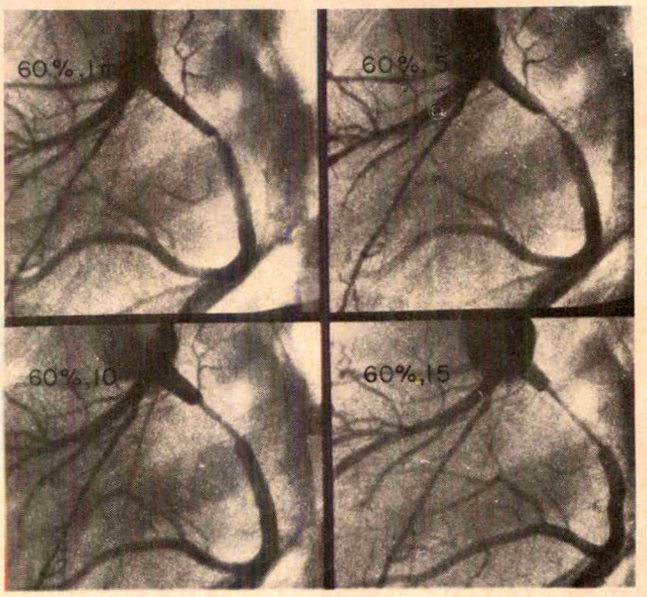


FIGURE 2. Coronary angiographic frames from a representative experiment as a 60 percent narrowing of the left circumflex artery is increased from 1 mm (**top left**) to 5 mm, 10 mm and finally to 15 mm long (**bottom right**). Note that these occluder sets allow smooth and uniformly calibrated reduction of vessel diameter as length is increased.

were evaluated as these narrowings were lengthened. Because the narrowings studied were acutely induced, our results should not necessarily be extrapolated to long-term narrowings in the dog or to acute or chronic disease in man.

Methods

Experimental model: The studies were made in 14 healthy mongrel dogs (20 to 30 kg). After premedication with morphine (1 mg/kg body weight) and pentobarbital (25 mg/kg) anesthesia, followed by an overnight fast, the animals were intubated. Respiration was controlled with a Harvard pump to maintain arterial blood gases and pH within the physiologic range. Through a left thoracotomy in the fifth intercostal space, the anterior descending or circumflex branch of the left coronary artery was approached. With the heart supported by a pericardial cradle, one of these branches was isolated by dissection. Only vessels averaging 3 mm or more in diameter over a length of 2 to 3 cm in their proximal portion were used. An appropriately sized cuff-type Narco Biosystems electromagnetic flow probe was positioned proximally around the artery to measure coronary blood flow (Fig. 1). Aortic pressure, used to assess proximal coronary arterial pressure, was measured through a saline-filled catheter placed in the ascending aorta after insertion through a femoral artery. In six animals, distal coronary pressure was measured through a no. 4 Teflon® catheter placed in a distal coronary branch (Fig. 1) beyond the flow probe and occluders. The pressure gauges (Statham P23Db) were made equisensitive by simultaneous calibration with the same test pressure using a Paley manifold. Pressure and flow signals and the electrocardiogram were monitored and recorded on an Electronics for Medicine model DR8 multichannel oscilloscopic recorder and on Hewlett-Packard model 3960 magnetic tape.

Coronary arterial narrowings: A snare was attached to a Starrett machinist's micrometer to create calibrated focal constrictions. The length of subsequently produced obstructions was controlled with plastic occluders made from Lucite® rods 5 mm in external diameter. From each piece, milled at a constant concentric internal diameter, a set of occluders was created by cutting various lengths ranging from 1 to 15 mm. This procedure ensured that within a set of occluders only the length varied. The occluders were positioned on the artery through a small tapering keyhole. Each stenosis (regardless of length) was applied for the same duration. Particular care was taken to avoid kinking and distortion; only when they were excluded by both inspection and subsequent angiography were the data accepted for final analysis.

Confirmation of the degree of coronary arterial narrowing: Two techniques were used to confirm that these occluders create precise narrowings of predicted caliber, smooth and regular throughout their length. Selective coronary cineangiography of the coronary narrowings produced with all the sets of occluders was performed in multiple projections (Fig. 2) and the diameters of the prestenotic and stenotic sections were measured with calipers. Postmortem polysulfide casts were also used to verify the degree of diameter reduction produced by the occluders, and the degree of diameter reduction was measured with calipers. At the conclusion of these hemodynamic studies, topical and intracoronary (5 to 10 mg) nitroglycerin was used in two animals to exclude the possibility of coronary spasm.

Data accumulation and analysis: Measurements were made from the mean flow and pressure signals averaged from at least 10 consecutive beats. Flow measurements were made at rest and during reactive hyperemia after a 10 second complete coronary occlusion. Percent repayment of flow debt was calculated according to Coffman and Gregg[10] as reactive hyperemic flow/flow debt × 100 by planemetric integration of

the mean flow signal. Flow debt = control flow rate × duration of occlusion. Reactive hyperemic flow = integral of flow curve during reactive hyperemia − (control flow rate × duration of reactive hyperemia).

In the analysis of the results, occlusions were grouped according to the nearest 10 percent reduction in diameter. Means and standard deviations were calculated for percent changes in mean coronary blood flows and resting pressure gradients at each diameter reduction for the snare narrowings and compared with the 40, 50 and 60 percent narrowings at each occluder length. An analysis of variance was used to determine the significance of the comparison between observations.

An example of a typical experiment: To find the reduction in diameter required to produce a "critical stenosis" the following procedure was used: "Critical stenosis" was defined as the stenosis at which a relatively small (10 percent) reduction in diameter caused a consistent decrease in pressure gradient and flow.[11] A series of constrictions of minimal length was produced by 10 percent decrements in diameter with the micrometer-fixed snare.[1] Flow and pressure signals were recorded with each change in diameter. Continuous measurements were made at rest and during reactive hyperemia after release of a 10 second distal coronary occlusion. This procedure was performed in duplicate, and from each series the "critical stenoses" for both resting and hyperemic flows were determined.

The influence of the length of the narrowings was then assessed. On the basis of the diameter narrowing necessary for "critical stenosis," a fixed narrowing was produced using a plastic occluder 1 mm long. Occluders were selected so that their internal diameter was greater than that found for "critical stenosis" for either resting or hyperemic flow. This usually resulted in a reduction in diameter of approximately 40 percent, but in each experiment the size of the narrowing produced by a given occluder could not be precisely confirmed until the verification studies described were performed. Only data from occlusions in the 40 to 60 percent range are included in this report. Resting and reactive hyperemic measurements made in duplicate were then repeated serially at this same reduction in diameter as the length of the narrowing was progressively increased to 5, 10 and 15 mm. Complete occlusions for the reactive hyperemic measurements were performed at least 5 minutes apart. This sequence was followed as the reductions in diameter were progressively increased with a different set of occluders until no flow was detectable. Records were accepted for analysis with each occluder in place only if heart rate and aortic pressure showed no significant change over at least 1 minute compared with the levels observed with no obstruction.

Results

Confirmation of degree of coronary arterial narrowing: Agreement between the degree of narrowing as measured with selective coronary cineangiograms and the postmortem polysulfide casts was ±5 percent. The degree of narrowing created with a 1 mm occluder, later confirmed with the techniques described, could be accurately (±10 percent) predicted during the experiment from its hemodynamic effects as assessed with responses observed with the calibrated snare. The coefficient of variation for the angiographic measurements ranged from 0 to 7 percent. The lower coefficient of variation was found for the longer narrowings.

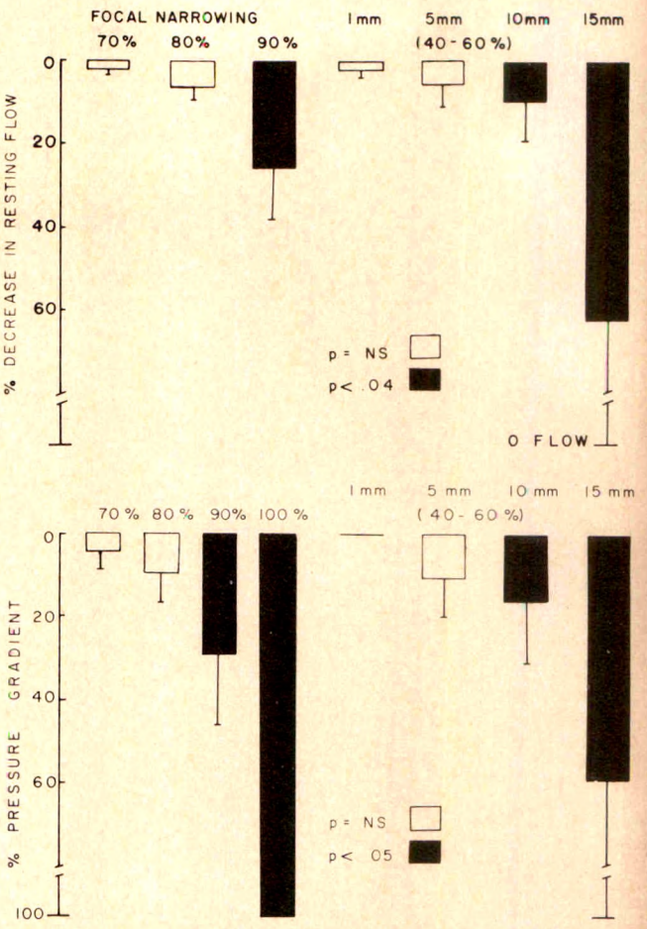


FIGURE 3. Summary of resting data on coronary flow (**top**) and pressure gradient (**bottom**) for short and long narrowings. Changes in flow (**vertical axis**) expressed as percent decrease (mean ± standard deviation) from that observed with short snare type narrowings are illustrated as occluder length progressively increases (**horizontal axis**). Note that resting flow decreases significantly at approximately 10 mm. Similarly, the pressure gradients (**bottom panel**) increase with longer occluders. Data obtained with snare narrowings are to the **left** and from the longer narrowings to the **right.** The data for all 40 to 60 percent narrowings are grouped together **at right.** Ao = aorta; CBF = coronary blood flow; Cor. = distal coronary; NS = not significant; p = probability.

Coronary blood flow and pressure at rest: Flow and pressure data obtained at rest are summarized in Figure 3. Because resting flow was significantly influenced with focal narrowings causing a greater than 80 percent reduction in diameter (Fig. 3, top) attention was focused on the effect of increasing lesser degrees (40, 50 and 60 percent) of coronary narrowing. There was a 5 percent (mean) decrease in flow from the levels achieved with snare or 1 mm narrowing as the length of narrowing was increased to 5 mm. Flow decreased 9 percent when the narrowing length was 10 mm and decreased 63 percent at 15 mm. Significant pressure gradients were found as the length of the narrowing increased (Fig. 3, bottom). These gradients, expressed as percent of the gradient at complete occlusion, aver-

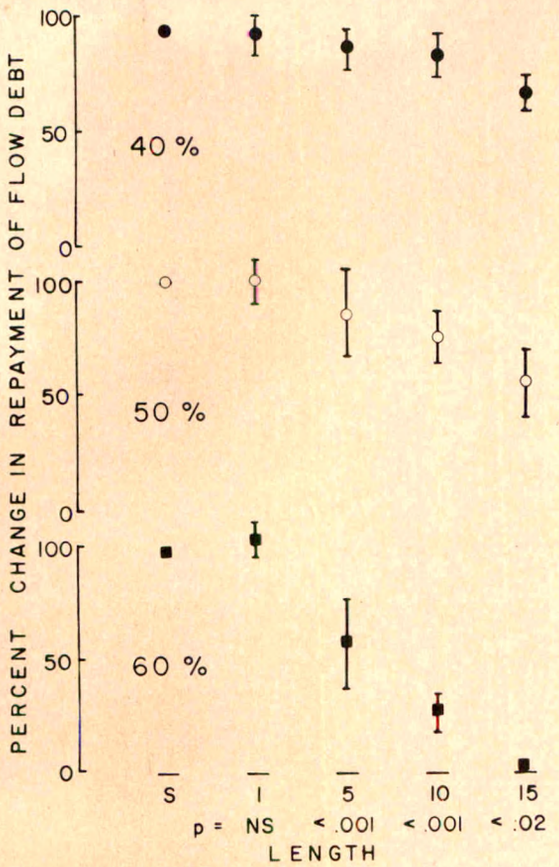


FIGURE 4. Summary of data obtained during reactive hyperemia. Percent changes in repayment of flow debt (**vertical**) for 40, 50 and 60 percent narrowings are considered separately. Narrowings created with the snare (S) are compared with measurements made with longer occluders (1, 5, 10 and 15 mm). Note that significant reduction in flow debt repayment occurs for all narrowings at these diameter reductions at a length of 5 mm, compared with snare-created or 1 mm long narrowings. The influence of length is more prominent with narrowings of 60 percent (**bottom**) than with those of 40 percent (**top**). NS = not significant; p = probability.

aged 9 percent when the narrowings were increased to 5 mm in length, 21 percent at 10 mm and 56 percent at 15 mm.

Flow reponses during reactive hyperemia: Repayment of flow debt occurring during reactive hyperemia at respective 40, 50 and 60 percent narrowings are shown in Figure 4. Snare and 1 mm long narrowings had similar flow responses for each degree of stenosis. For all such narrowings, percent flow debt repayment decreased a mean of 25 percent when the occlusion was lengthened to 5 mm, 41 percent at 10 mm and 58 percent at 15 mm by comparison with flow responses observed with snare-created narrowings of the same diameter. Examples of these responses to progressive lengthening of a 60 percent reduction in diameter compared with short narrowings produced by snare are shown in Figures 5 and 6.

Discussion

The definition of significant coronary arterial narrowing is not clear. Different experimental models have been used to study the hemodynamic influence of stenoses in vitro and in vivo. The former models offer precise control of proximal driving pressure and distal resistance. But extrapolation to a pulsatile circulation with a dynamic peripheral resistance is difficult. Observations concerning the hemodynamic significance of the length of a narrowing from in vitro studies are conflicting. Logan[12] varied the length of narrowing from 1 to 3 mm and found no significant hemodynamic effect, but others[13–15] increased length 4- to 10-fold and suggested that flow was affected. Noncoronary in vivo studies have generally implied that length may be an important variable.[16–18] One study[18] found that increasing the length of 60 percent reductions in diameter from 1 to 8 cm decreased flow and increased the pressure gradient comparable with levels in short 80 to 90 percent narrowings in the dog abdominal aorta.

In vivo coronary arterial studies have suggested that reductions of 50 to 90 percent in diameter may affect resting and stimulated flow and pressure. These seemingly conflicting conclusions were drawn from data obtained from similar preparations (open chest dogs), but differences in the techniques used to create the coronary narrowings may explain the variability. Snare type narrowings (presumably less than 1 mm long) were used by some,[1,2] who concluded that large reductions (85 to 90 percent) in diameter were necessary to affect resting coronary flow. Longer (2 to 9 mm) plastic occluders were used by others.[19–23] With longer occluders, resting coronary flow decreased with lesser degrees of narrowing (50 to 75 percent) than with snare type occluders. The possible importance of both length and degree of narrowing, particularly during reactive hyperemia, was suggested recently.[21–23] We found that a reconsideration of the cited studies in relation to occluder length unifies these seemingly conflicting data on the degree of narrowing necessary to reduce coronary flow (Fig. 7).

Coronary flow with short versus long coronary arterial narrowing: Our study adds support to the concept that the length of obstruction is an important factor in the significance of a given coronary narrowing. A prerequisite to these experiments was the confirmation of coronary hemodynamic findings relative to short narrowings. In this regard, resting (low flow rate) and reactive hyperemic (high flow rate) flows are maintained until luminal diameter is reduced, respectively, more than 80 percent and approximately 50 percent. Our findings indicate that increasing the length of short 40, 50 and 60 percent obstructions to 5 mm further decreases reactive hyperemic flow (Fig. 4). As the length of narrowing is increased to 10 and 15 mm and the reduction in diameter held constant, resting flow also decreases and the pressure gradient between the aorta and distal coronary artery increases (Fig. 3). Thus, long narrowings in the range of reduction in diameter often considered insignificant (40 to 60 percent) can alter coronary hemodynamic responses at rest and during hyperemia (Fig. 5).

Potential factors altering coronary flow responses: Several possibilities that could alter the observed flow responses independently of the narrowing

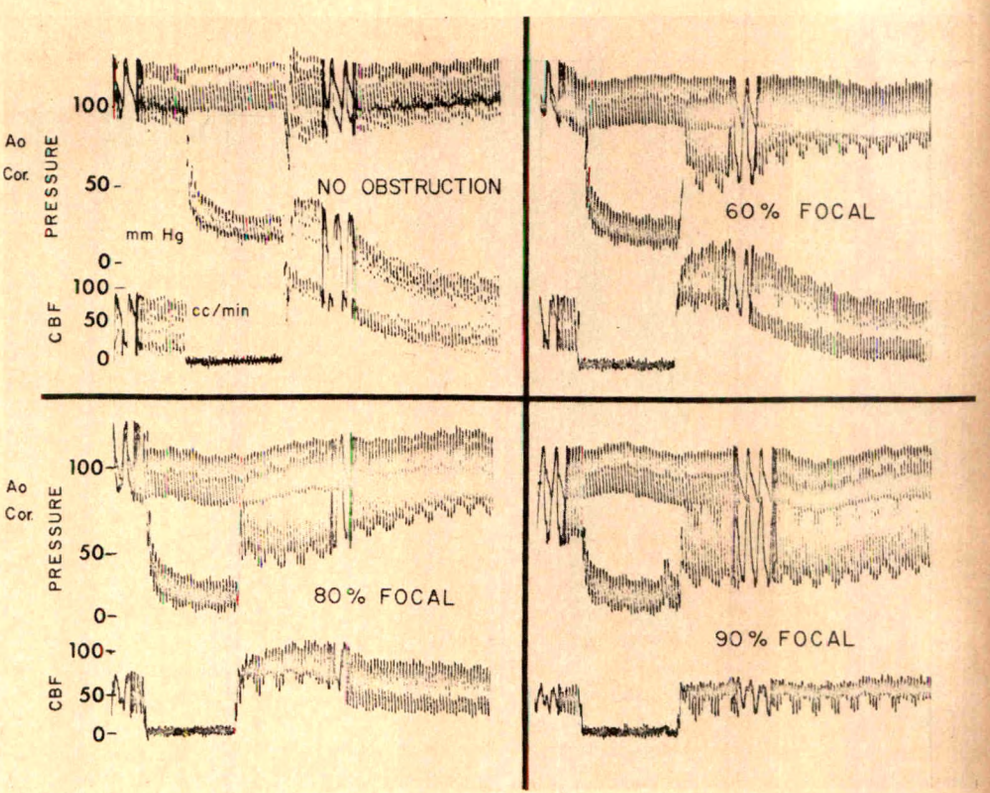


FIGURE 5. Examples of pressure and flow responses to short (focal) coronary narrowings. Coronary flow with aortic (Ao) and distal coronary (Cor.) pressures without obstruction (**upper left panel**) shown from a typical experiment. Resting peak coronary blood flow (CBF) is 74 cc/min and the pressures are similar. During a 10 second complete occlusion, flow ceases abruptly as an 80 mm Hg pressure gradient develops. After release of occlusion, peak hyperemic coronary blood flow occurs promptly as distal coronary pressure returns toward the level of aortic pressure. (The record was cropped for illustration.) Changes associated with a series of increasing snare narrowings are shown in the other panels. With a short 60 percent narrowing (**top right**) the resting coronary blood flow and pressure gradient are similar to values during the period of no obstruction, but peak hyperemic flow is delayed and less than with no obstruction. Increasing the short obstruction to 80 percent (**bottom left**) decreases resting coronary blood flow and increases the pressure gradient. Decreased and prolonged reactive hyperemic coronary blood flow occurs. When the obstruction is increased to 90 percent (**bottom right**), there is additional reduction in coronary blood flow with a much larger pressure gradient. Reactive hyperemic flow is greatly reduced.

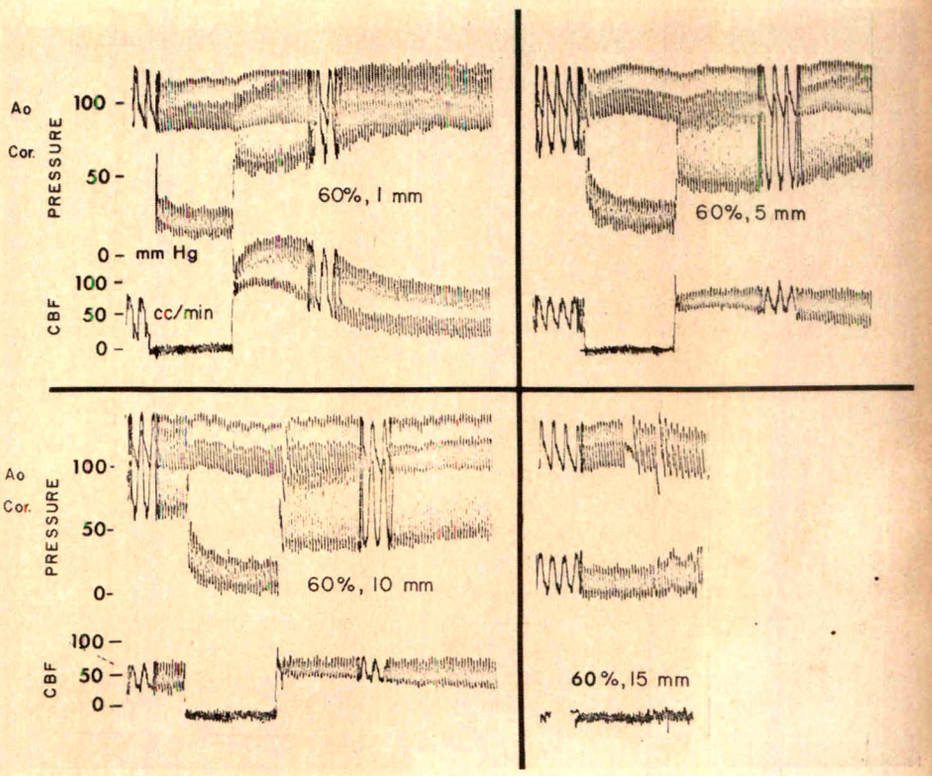


FIGURE 6. Examples of pressure and flow responses to long coronary narrowings in the same animal whose data are shown in Figure 5. The 1 mm long 60 percent narrowing (**top left**) has hemodynamic properties similar to those of the 60 percent focal narrowing in Figure 5, top right. Peak reactive hyperemic flow is only minimally decreased and its peak is later. Increasing the length of narrowing to 5 mm (**top right**) decreases resting coronary blood flow (CBF), and a large diastolic pressure gradient develops. Reactive hyperemic flow is decreased and prolonged. Increasing the length of narrowing to 10 mm (**bottom left**) causes a further decrease in resting coronary blood flow as both systolic and diastolic pressure gradients occur and only minimal reactive hyperemic coronary blood flow results. Note the similarity to the short snare-produced 90 percent narrowing (Fig. 5, bottom right). With a 15 mm long narrowing (**bottom right**), coronary blood flow is markedly reduced and there is a large pressure gradient similar to that observed with the complete occlusion used to produce reactive hyperemia. Abbreviations as in Figure 5.

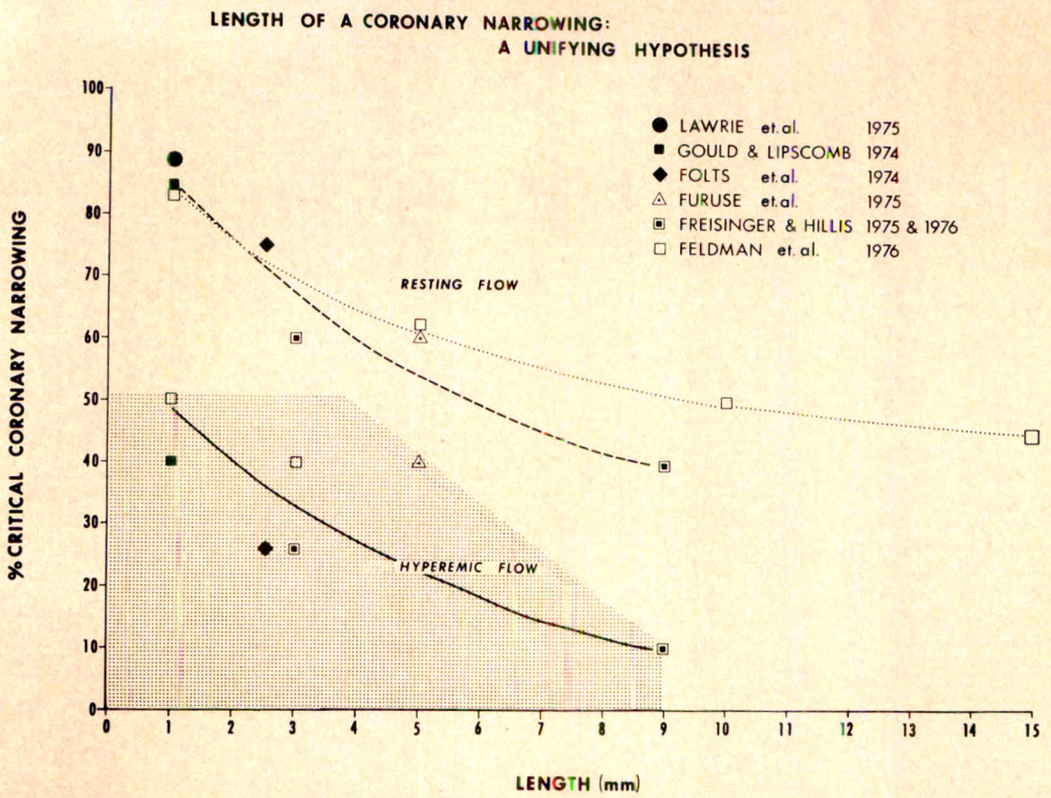


FIGURE 7. The unifying role the narrowing length plays in the determination of critical coronary narrowing. Data at rest and during reactive hyperemia from other investigations[1,2,19–21] were analyzed with regard to length of narrowing (**horizontal axis**) and plotted at the reduction in diameter reported to alter flow significantly (**vertical axis**). Our data are added to this framework, and it is apparent that consideration of the length of the narrowing solidifies the concept of "critical narrowing" (**dashed line**).

length are worthy of consideration. Among these is the possibility that the plastic occluders distort the vessel causing uneven obstruction to a greater degree than predicted. Distortion was not visualized in the angiograms as narrowing length increased (Fig. 2). Angiographic predictions of the degree of obstruction obtained with these long narrowings related closely to actual measurements. The casts also permitted a more detailed study of cross sections of the narrowed segment. Within the limitations of these techniques we found no evidence suggesting that other possible occluder-related influences such as kinking or distortion were present. No evidence was present to suggest spasm. Even the administration of nitroglycerin with the occluder in place resulted in no significant coronary hemodynamic or angiographic changes, thus further excluding the possibility of occluder-related spasm. Concern that variation in the duration of occlusion could alter flow responses independently of the degree and length of the stenosis was avoided because each occlusion was maintained for the same duration.

In addition to narrowing characteristics, possible changes in blood pressure, heart rate and distal bed resistance could affect coronary hemodynamics. Experiments were accepted for analysis only when blood pressure and heart rate did not vary significantly. However, distal coronary resistance was not controlled and would be most operative at rest and least operative during reactive hyperemia.[10,24] Observations made during reactive hyperemia, presumably at near maximal vasodilation, would tend to minimize the influence of distal bed resistance.

Predicting coronary flow relative to narrowing: Several formulas for predicting blood flow in arteries have been proposed. A modified Poiseuille equation did not predict the magnitude of the changes in flow and pressure we observed with different degrees and length of narrowings.[11,25] Lawrie et al.,[2] using Bernoulli's theorem, developed an equation for the coronary circulation but ignored the importance of narrowing length. Berger and Wang[11] theoretically predicted a family of curves relating degree of narrowing and flow. Our observations suggest that similar predictions may be valid when degree and length of a narrowing are considered simultaneously.

Clinical implications: Caution should be exercised when attempting to extrapolate animal data in order to predict possible hemodynamic consequences of coronary artery disease in man. Qualifications are also necessary relative to inferences drawn from acute versus chronic narrowing. Irregular atherosclerotic plaques differ from the "ideal narrowings" created with plastic

occluders. With the former conditions, the blood flow pattern may be altered. The possible damping effect of stenosis and the suggestion that turbulent flow does not occur in coronary arteries[3] are additional considerations. Moreover, in the clinical setting the significance of a narrowing is also influenced by potential compensatory mechanisms that include collateral vessels; therefore direct application of our data is not possible. Nevertheless, we conclude that the length of a coronary arterial narrowing is an important consideration in determining the hemodynamic significance of a given coronary obstruction.

Acknowledgment

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Effects of Lidocaine on Hypoxic and Ischemic Cardiac Cells

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Cardiac cells severely affected by ischemia or hypoxia were exposed to lidocaine in vitro while intracell and extracell potentials were recorded. Endocardial preparations dissected from normal dog hearts were superfused with physiologic solutions of low oxygen content until myocardial cells were partially depolarized and generated poor action potentials. Purkinje fibers were slightly altered. Epicardial preparations dissected from infarcted dog hearts to include both normal and ischemic regions were superfused with physiologic solutions of normal oxygen content. The ischemic cells were partially depolarized and generated poor action potentials. In both types of preparations, conduction was very slow and irregular but abnormal automaticity was not observed with intracell recordings. However, abnormal spontaneous firing occurred. Lidocaine in therapeutic concentrations (1.1 or 2.2 $\times$ 10^{-5} molar) invariably abolished propagated action potentials in severely affected cells and modestly reduced membrane responsiveness in cells that were nearly normal. Concomitantly, abnormal spontaneous beats disappeared with exposure to lidocaine. The recovery of responsiveness of abnormal cells was greatly prolonged by lidocaine, and strength-interval curves were shifted upward and to the right. Tetrodotoxin (5 $\times$ 10^{-7} g/ml) markedly depressed or abolished the action potentials of the severely affected cells. It is concluded that lidocaine abolished abnormal spontaneous beats by extinguishing very slow conduction resulting from depressed fast channels.

The remarkable potency of lidocaine in the suppression of ectopic ventricular beats has been a boon to clinicians and a challenge to basic scientists in search of mechanisms. Lidocaine has generated discussion and controversy since the appearance of early studies indicating that it did not share with prototype antiarrhythmic agents certain supposedly important properties. It was claimed that lidocaine, in therapeutic concentrations, did not depress membrane responsiveness and conduction velocity,[1–5] did not prolong refractoriness[1–3,6,7] and had relatively little effect on excitability.[4] However, later studies necessitated revision of these original assessments. It was shown that membrane responsiveness is depressed by lidocaine if the extracell concentration of potassium is normal or high.[8–10] The higher the level of potassium and the more depolarized the cells, the greater is the depression of membrane responsiveness.[11] If responsiveness and excitability are depressed by hypoxia, these properties are further depressed by lidocaine to a greater degree than in normal cells.[12] Slow conduction in ischemic myocardium is slowed further by lidocaine whereas conduction in normal myocardium is unaffected.[13]

The significance of these findings in relation to the antiarrhythmic effect of lidocaine is unclear. Depression of responsiveness and slowing of conduction by lidocaine should enhance the potential for reentrant ectopic beats. In previous reports, the cardiac cells exposed to lidocaine

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were not definitely implicated in the generation of arrhythmias. Consequently, we undertook to study the electrophysiologic effects of lidocaine on cardiac cells severely affected by ischemia or hypoxia to the extent that abnormal spontaneous beats were generated.

Methods

Preparation of ischemic and aortic tissues: Hearts were excised from 30 mongrel dogs anesthetized with sodium pentobarbital (30 mg/kg body weight intravenously). Preparations containing Purkinje and myocardial cells were dissected from the endocardial surface. Thirty other animals were similarly anesthetized with sodium pentobarbital, mechanically ventilated and the left anterior descending coronary artery was ligated 1 to 2 cm from its origin through a left thoracotomy incision. The incision was reopened under pentobarbital anesthesia 1 to 3 days later, and the heart excised. Preparations containing both normal and ischemic myocardium were dissected from the epicardial surface. The ischemic myocardium was distinguishable by its pale and hemorrhagic surface.

The preparations were superfused at 35–37° C with a physiological solution of the following composition (millimolar): sodium ion 151.1, potassium ion 4.05, calcium ion 1.35, magnesium ion 0.5, chloride ion 131.25, bicarbonate 24.0, dibasic phosphate 1.8 and dextrose 5.5. In the hypoxia experiments, the chamber volume was 2.0 ml and the flow rate was 10 ml/min. The solution was equilibrated with a gas mixture of 95 percent oxygen and 5 percent carbon dioxide or 95 percent nitrogen and 5 percent carbon dioxide. When the mixture of nitrogen and carbon dioxide was used, the partial pressure of oxygen (PO_2) of the superfusate aspirated from just above the surface of the preparations, was between 30 and 70 mm Hg. When the oxygen carbon dioxide mixture was used, the PO_2 was between 300 and 400 mg Hg. Lidocaine was added to the superfusate in concentrations of 1.1×10^{-5} molar or 2.2×10^{-5} molar (2.5 or 5.0 μg/ml), which were chosen because they are within the therapeutic range of concentrations.[14,15] Tetrodotoxin was used in a concentration of 5×10^{-7} g/ml.

Electrophysiologic studies: The tissues were stimulated by means of rectangular current pulses of variable frequency, duration and amplitude (up to 30 ma), delivered from pulse generators triggered by ramp generators through a stimulus isolation unit (Tektronix series 2600). The usual driving cycle lengths were in the range of 1,000 to 3,000 msec. Extrastimuli with variable amplitude and duration could be inserted every 10th cycle. The stimulating current was calculated from the voltage, measured with a differential amplifier, across a known resistance (100 ohms) in series with one of the stimulating electrodes. In the experiments with hypoxia, deterioration of the preparations was hastened by rapid pacing at driving cycle lengths between 400 and 200 msec. When electrophysiologic abnormalities became apparent, the driving cycle lengths were increased to 1,000 to 3,000 msec.

Intracell and extracell potentials were recorded with standard techniques. Intracell potentials were recorded through machine-pulled glass microelectrodes with tip resistance of 10 to 30 megohms when filled by boiling with 3 molar potassium chloride. The first stage amplifier had high impedance (10^{14} ohms), negative capacitance feedback and gain of 10. Extracell potentials were recorded with bipolar electrodes of fine (diameter 0.003 inches [0.00762 cm]), Teflon®-coated stainless steel wires bared at the tips. The wires were led into condensor-coupled differential amplifiers with gain of 200. The preamplified signals were led into an oscilloscope with eight input channels and a dual time base (Tektronix series 5100). The upstrokes of action potentials were differentiated with a resistance-capacitance circuit or operational amplifier that was linear up to 1000 v/sec. Conduction was assessed by measuring conduction times and distances between sites of recording and stimulation. The durations of action potentials were measured to 100 percent repolarization.

To focus on cardiac tissues that could be strongly implicated in the production of ectopic ventricular beats, we confined our analysis primarily to preparations of the following types: (1) Ischemic epicardial preparations that were excised from hearts manifesting spontaneous ectopic ventricular beats in vivo and that showed spontaneous (unstimulated) action potentials in vitro. (2) Hypoxic endocardial preparations that manifested irregular spontaneous action potentials at rates exceeding 50 beats/min. In our laboratory, epicardial preparations from normal hearts under normal conditions of superfusion do not fire spontaneously except in the first 5 minutes after isolation. Normal endocardial preparations may fire regularly at rates that do not exceed 40/min.

Definitions: In this report, *membrane responsiveness* refers to the relation between maximal upstroke velocity (V̇max) and the membrane potential at excitation. *Recovery of re-*

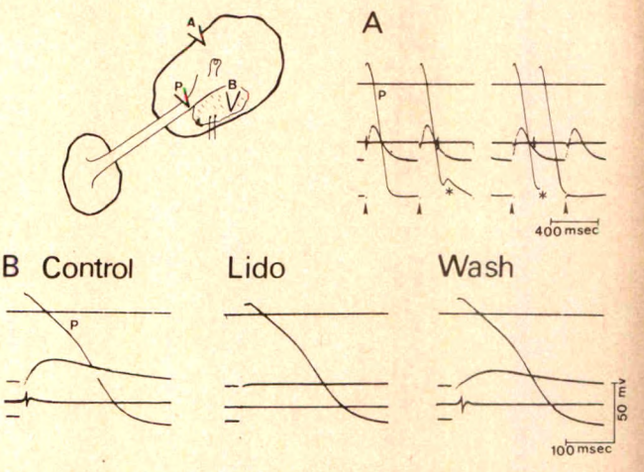


FIGURE 1. Suppression of spontaneous beats by lidocaine concomitant with the abolition of responses in abnormally depolarized cells. The sketch of the preparation shows an island of septal myocardium **(upper left)** joined by a Purkinje (P) strand to an island of papillary muscle. Intracell recording sites at A and B are depicted by **acute angles,** extracell sites by **parallel bars** and the site of stimulation by a **coil.** A region of intermittent marked delay of activation in myocardial cells is **outlined** and **hatched** in the sketch. In **Panel A,** intracell recordings from a Purkinje fiber showed spontaneous (unstimulated) responses (marked by **asterisks**). The stimuli are marked by **arrow heads.** The **top tracing** marks the level of 0 potential. The spontaneous Purkinje responses were associated with intermittent marked delay of the driven electrograms **(second tracing)** recorded from the hatched region. The intracell recordings **(third tracing)** from an abnormally depolarized myocardial cell (A) in another part of the preparation did not show marked delay of activation. In **Panel B,** the microelectrode was moved to a site (B) in the region **(hatched)** showing intermittent delay in order to monitor intracell potentials in that region. The electrogram and Purkinje (P) recordings (the third and fourth tracings, respectively, in **Panel B**) were from the same sites as in **Panel A.** Lidocaine (Lido) abolished the propagated responses and the spontaneous beats. Repeat superfusion without lidocaine (Wash) resulted in restoration of responses in the depressed region.

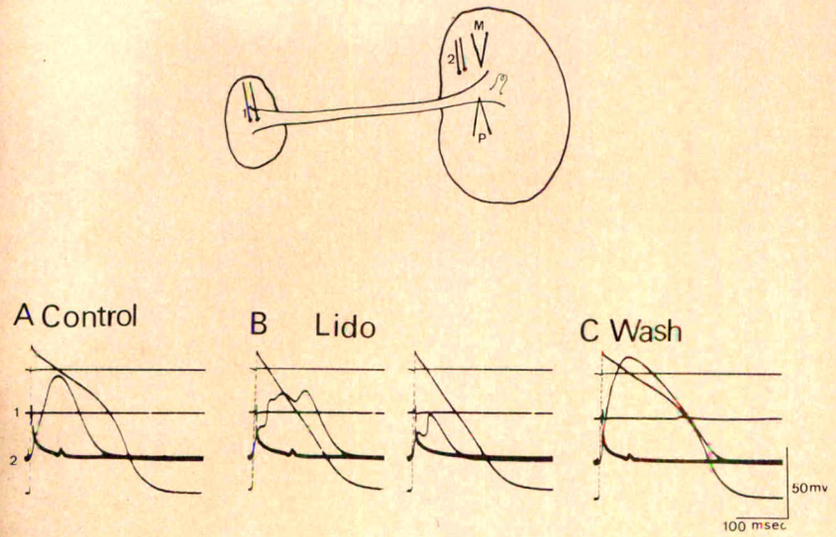


FIGURE 2. Depression of responses of abnormally depolarized myocardial cells by lidocaine, 2.2×10^{-5} molar. Transmembrane potentials of a Purkinje fiber (P), a myocardial cell (M) and electrograms recorded from myocardial cells (2) of the proximal island and Purkinje strands (1) of the distal island are shown before **(A)**, during **(B)**, and after **(C)** exposure to lidocaine. Bipolar recording 2 shows a large stimulus artifact preceding the myocardial spike. Earlier and later phases of lidocaine effect are shown in **B.** The diminutive intracell response after lidocaine **(B,** right) was not propagated and not reflected in the electrogram. Conduction velocity across the Purkinje strand was unaffected. Symbols and abbreviations as in Figure 1.

sponsiveness refers to the time-dependent process of restoration, after a prior excitation, of the capacity to generate an upstroke of maximal amplitude and velocity in relation to a given membrane potential at excitation. *Steady state responsiveness* is membrane responsiveness determined after recovery of responsiveness is complete. *Repolarization responsiveness* is membrane responsiveness during repolarization. In normal myocardial cells, there is a difference between repolarization responsiveness and steady state responsiveness[16] due to a small delay of full recovery of responsiveness beyond the termination of repolarization. In abnormal cells or cells affected by lidocaine, the difference between repolarization responsiveness and steady state responsiveness may be marked because delay in recovery beyond the termination of repolarization may be substantial. The term "post repolarization refractoriness" has been used previously in referring to this delayed recovery.[17]

Results

Hypoxic Endocardial Preparations

With exposure to the nitrogen-carbon dioxide mixture, the depressant effects of hypoxia were not entirely uniform throughout the preparation. Myocardial cells were always affected more severely than Purkinje cells. Myocardial cells were affected variably in different portions of the preparation, perhaps dependent on differing thickness of the endocardium or differing PO_2 values within the chamber. After exposure of the preparation to the hypoxic solution, the myocardial cells were partially depolarized and generated action potentials of diminished amplitude and velocity.

Abnormal spontaneous firing: In 13 of 30 preparations, abnormal spontaneous firing developed. An example of abnormal spontaneous firing in an endocardial preparation is shown in Figure 1A. This preparation had been exposed to hypoxia for 2 1/2 hours. The Purkinje action potentials (Fig. 1A and B) were affected slightly. Vmax was reduced to 365 v/sec from a control value of 413 v/sec. Diastolic depolarization was not enhanced. On the other hand, myocardial cells were depolarized to levels of resting potential between −55 and −70 mv and generated severely depressed responses, exemplified by the diminutive action potentials in Figure 1,A and B, which represent recordings from two separate myocardial cells (A and B in sketch). There was intermittent spontaneous premature excitation of the Purkinje fibers, which was invariably preceded by greatly delayed activation of myocardial cells in a certain region of the preparation (hatched region in sketch) monitored by the bipolar electrogram. The diminutive action potential in Figure 1A was recorded from a depressed myocardial cell in a region that did not show intermittent marked delay of activation despite the severe depression of the cells. In the recordings in Figure 1B, one intracell and one extracell, from depressed myocardial cells within the suspect reentry pathway (hatched region) are shown along with the Purkinje recording during the administration of lidocaine (1.1×10^{-5} molar). Lidocaine abolished propagated responses in the depressed myocardial cells and concomitantly abolished the spontaneous beats. The Purkinje cell was affected little by lidocaine. In all hypoxic preparations, lidocaine abolished abnormal spontaneous beats as well as propagated responses in severely depressed myocardial cells.

Action potentials of affected myocardial cells: During the early exposure to lidocaine, the action potentials of affected myocardial cells were progressively diminished, deformed and delayed on route to extinguishment with little

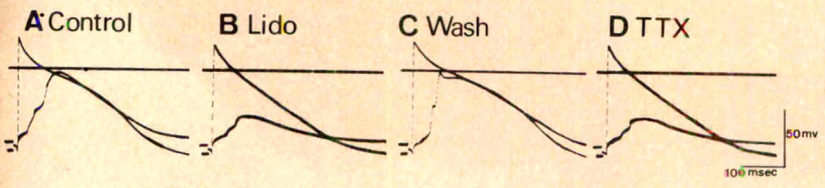


FIGURE 3. Comparison of the effects of lidocaine, 1.1×10^{-5} molar, and tetrodotoxin (TTX) on hypoxic myocardial and Purkinje cells. Myocardial cells were more severely affected than the Purkinje cells after 2 hours and 12 minutes of hypoxia. Abbreviations as in Figure 1.

change in resting potential. An example of progressive deterioration of action potentials under the influence of lidocaine (2.2×10^{-5} molar) is shown in Figure 2. The Purkinje fiber was nearly normal but the myocardial cell was severely affected after 3 hours of hypoxia. The resting potential of the myocardial cell was −65 mv; the action potential had a slow upstroke (0.8 v/sec); and conduction was very slow. The conduction time to the site of recording of the electrogram, which was 5 mm from the stimulating electrodes, was 78 msec. Lidocaine greatly attenuated the action potential and abolished the electrogram (Fig. 2B). Note the bizarre upstrokes of the action potentials during the progression of lidocaine effect. The upstroke of the Purkinje fiber was minimally affected, and conduction velocity down the strand was unchanged.

Tetrodotoxin: Six of the hypoxic preparations exposed to lidocaine were subsequently exposed to tetrodotoxin. In every instance, the abnormal responses that were abolished or greatly attenuated by lidocaine were similarly affected by tetrodotoxin. Recordings from a representative experiment are illustrated in Figure 3.

Refractoriness in hypoxic cells: Lidocaine produced a prolongation of refractoriness in hypoxic cells as evaluated in the conventional manner (that is, in relation to the time course of threshold stimulus strength after a prior excitation). Figure 4 shows the effects of lidocaine on the strength-interval curves for both anodal and cathodal stimuli applied at the same site during normal oxygenation and during hypoxia. Lidocaine slightly increased the late diastolic stimulus threshold in normal fibers but raised the threshold more with shorter coupling intervals. In the hypoxic fibers, lidocaine greatly shifted the strength-interval curves upward and rightward. Especially prominent was a prolongation of the period of inexcitability (absolute refractory period) that extended well beyond the termination of the action potentials. Similar results were obtained in six other experiments.

Induction of spontaneous beats by lidocaine: Some preparations were exposed to lidocaine during early phases of hypoxia when the myocardial cells were not severely depressed and spontaneous beats were absent. In one of those exposures, lidocaine appeared to induce abnormal spontaneous beats. Recordings from that hypoxic preparation, before and after exposure to lidocaine, are shown in Figure 5. In this preparation, the stimulus directly excited Purkinje cells at the base of the free strand, which in turn activated ventricular myocardial cells. During early exposure to lidocaine, there was progressive delay in activation of myocardial cells of the preparation. When the delay exceeded the refractory period

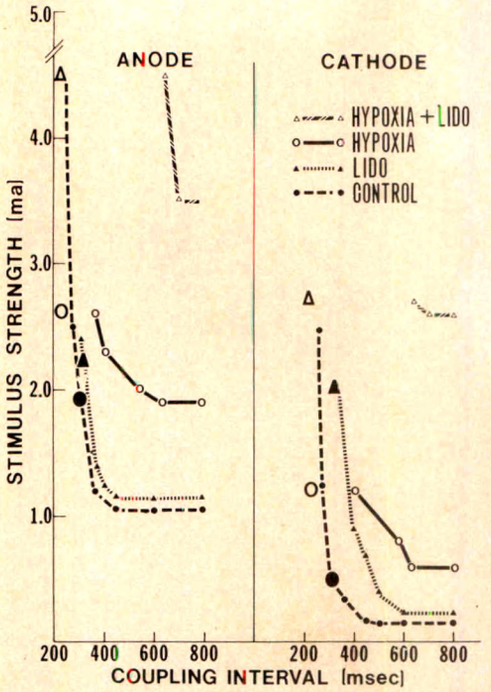
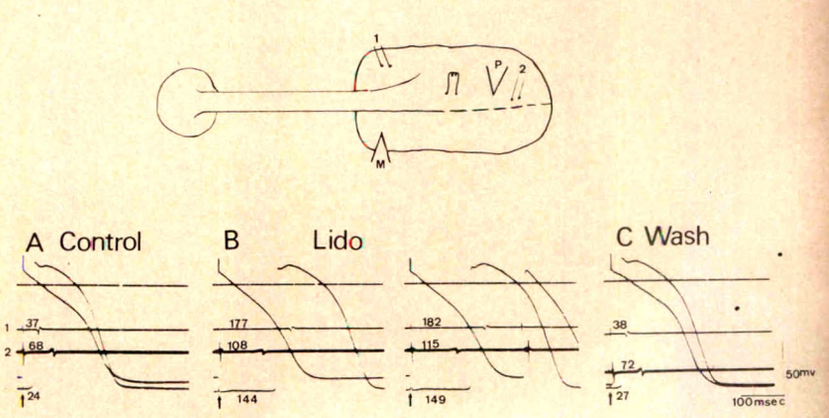


FIGURE 4. Strength-interval curves of normal and hypoxic myocardial cells exposed to lidocaine, 2.2×10^{-5} molar. The larger symbols denote the durations of action potentials in the immediate vicinity of the stimulating electrodes for each curve with the corresponding smaller symbols. Abbreviation as in Figure 1.

of the Purkinje fibers, they were reexcited (Fig. 5B). Note that the action potentials of the monitored cells were nearly normal and altered only slightly by lidocaine. Presumably, there was a locus of abnormal cells somewhere in the pathway between the Purkinje fibers and the ventricular myocardial cells. Conduction must have been selectively slowed in this abnormal locus by lidocaine. Conduction across the Purkinje fiber was unaffected. During the washout of lidocaine, the conduction delay of myocardial cells diminished and the spontaneous reexcitation of Purkinje fibers disappeared. In 32 exposures of mildly hypoxic preparations to lidocaine, we observed this phenomenon (the induction of spontaneous beats by lidocaine) only once.

FIGURE 5. Spontaneous reexcitation of Purkinje cells related to marked delay of activation of myocardial cells induced by lidocaine, 1.1×10^{-5} molar. Times of activation of myocardial cells at various recording sites are shown. Extracell recordings (1 and 2) contain both Purkinje and myocardial electrograms distinguishable by their different durations. The **interrupted line** in the **sketch** denotes the posterior border of the main bundle branch on the upper section. Symbols and abbreviations as described in Figure 1. In the septal island (to the right of sketch), Purkinje-myocardial junctions appeared to be confined to the left end of the island as it appears on the sketch. This was the region of earliest activation and myocardial activation appeared to proceed from this locus generally upward and to the right in the septal island.



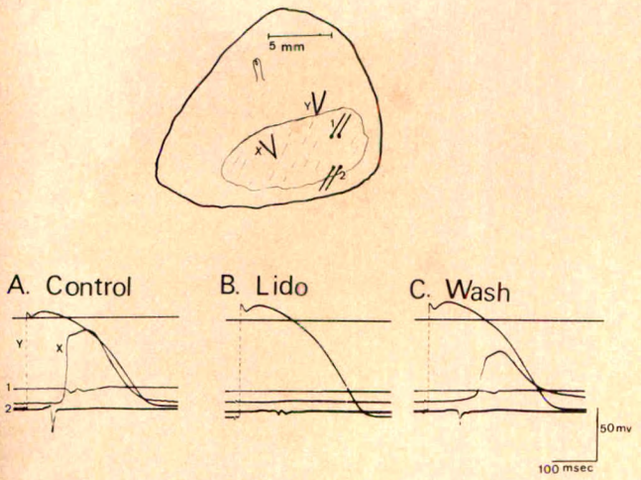


FIGURE 6. The effects of lidocaine, 2.2×10^{-5} molar, on ischemic myocardial cells. Transmembrane potentials (X and Y) and electrograms (1 and 2) were recorded from various sites in the ischemic zone and the normal zone near the border. In the **sketch** of the preparation, the ischemic zone is **outlined** and **hatched. Panel C** was recorded before the washout of lidocaine was complete, but does show some recovery toward control level. Note that both intracell (X) and extracell (1) potentials from the interior of the ischemic zone were abolished by lidocaine. Less severely affected border sites (Y and 2) continued to respond during lidocaine exposure. Symbols and abbreviations as in Figure 1.

Ischemic Epicardial Preparations

Lidocaine and propagated responses in ischemic zone: In these preparations, cells in the ischemic zone were heterogeneously abnormal, showing partial depolarization and slow upstrokes. Our usual procedure was to search out regions in the ischemic zone with the poorest responses and most delayed activation. The effects of lidocaine on responses in such regions were usually compared with the effects on less abnormal cells at the borders of the ischemic zone or cells in the normal zone. The abolition of spontaneous beats by lidocaine was always accompanied by abolition of responses and elimination of propagation in the more abnormal regions of the ischemic zone. Action potentials of myocardial cells in normal or border zones were minimally affected by lidocaine. Figure 6 contains recordings from ischemic and border zones of an epicardial preparation before, during and after exposure to lidocaine, 1.1×10^{-5} molar. The response of the cell within the ischemic zone was abolished but the cell in the border zone was minimally affected. Also, the electrograms within the ischemic zone were attenuated or abolished in proportion to the severity of abnormality before exposure. Five preparations were exposed to tetrodotoxin as well as lidocaine. In each case, propagated responses were abolished in severely depressed cells of the ischemic zone.

Lidocaine and impaired membrane responsiveness: The responses of the two cells in Figure 6 were quite different although the difference in resting potentials was only about 5 mv. This observation suggested that responses of ischemic cells might be depressed by factors other than the decrease by ischemia. This impairment of responsiveness of ischemic cells sometimes was highlighted by simultaneous recordings of cells with virtually the same resting potential but very different action potentials. Such a comparison is shown in Figure 7. The ischemic cell was not much depolarized but the amplitude and upstroke velocity of the action potentials were diminished compared with the cell in the border zone. The cell with prior impairment of responsiveness was more sensitive to lidocaine (Fig. 7B). Thus the heightened sensitivity to lidocaine was dependent not solely upon partial depolarization but also upon prior impairment of responsiveness.

Lidocaine and recovery of responsiveness: Cells with impaired responsiveness also had slow recovery of responsiveness. Lidocaine produced further delay in recovery. The

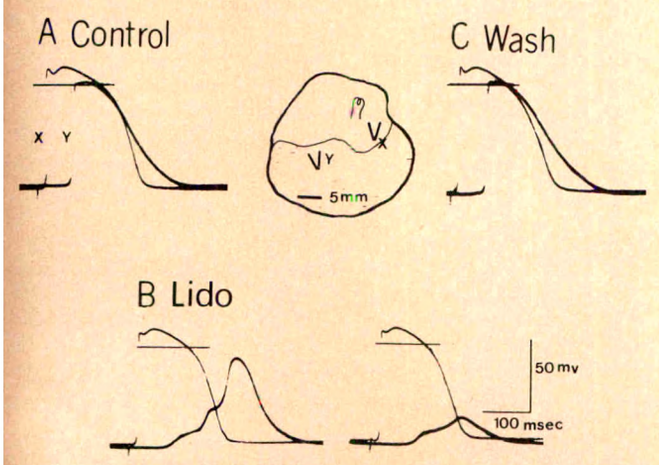


FIGURE 7. Differential effects of lidocaine, 1.1×10^{-5} molar, on ischemic (Y) and normal (X) myocardial cells with similar resting potentials. The resting potential of the cell in the ischemic zone was −75 mv but it had a poor action potential compared with the cell in the normal zone near the border. The $\dot{V}$max of the cell at site Y was 18 v/sec, whereas at site X it was 110 v/sec. The "normal" cell may have been mildly depressed by virtue of being near the border of the infarct. The ischemic zone is at the bottom of the **sketch.** Symbols and abbreviations as in Figure 1.

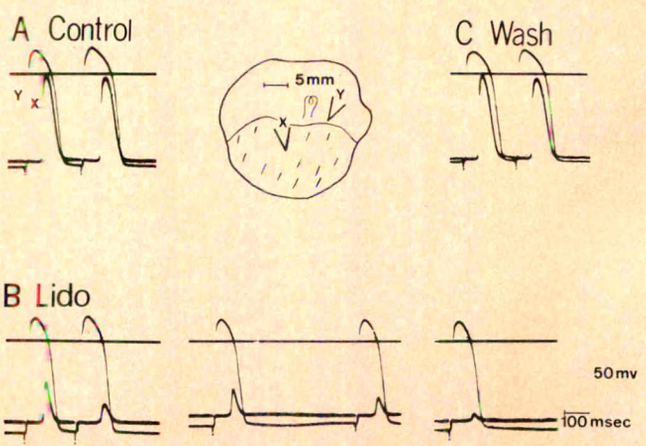


FIGURE 8. Differential effect of lidocaine, 1.1×10^{-5} molar on recovery of responsiveness of myocardial cells severely (X) and moderately (Y) affected by ischemia. The responsiveness of the cell in the ischemic zone was nearly fully recovered at a coupling interval of 220 msec for the extrastimulus. Exposure to lidocaine **(B)** greatly delayed recovery of responsiveness and, finally, greatly attenuated the driven response. The driving rate was 20/min. Symbols and abbreviations as in Figure 1.

depressant effect of lidocaine on recovery was exaggerated in the more abnormal cells, as illustrated by the recordings from two cells shown in Figure 8. In this experiment, the more depressed cell required about 220 msec for full recovery of responsiveness before exposure to lidocaine (Fig. 8A). During exposure to lidocaine, full recovery of responsiveness was not complete after 600 msec in this cell (Fig. 8B, middle). There was progressive depression of the driven response concomitant with the delay of recovery to the point where the driving and extrastimuli failed to elicit propagated responses. After lidocaine, full recovery was usually not attained during the driving cycle; that is, the latest possible extrastimulus remained diminished compared with the driven response. The delay in recovery produced by lidocaine appeared to be proportional to the severity of depression of the driven response before lidocaine (compare the effects of lidocaine on the two cells in Figure 8).

Discussion

There appears to be substantial evidence that lidocaine in the therapeutic concentration range depresses membrane responsiveness of normal cardiac cells if the potassium concentration is in the normal range.[8–11] However, this effect has little if any influence on conduction in the specialized conduction system or in the myocardium of normal hearts.[4,5,13] On the other hand, if cells are partially depolarized by potassium,[11] hypoxia[12] or ischemia,[13,18,19] lidocaine will depress responsiveness more than in normal cells and it will slow conduction further. These experimental findings are supported by reports of dangerous impairment of conduction by lidocaine administered to patients with disease of the specialized conduction system.[20,21]

Depressant effects of lidocaine versus its antiarrhythmic action: These observations confer upon lidocaine properties that are generally considered important for antiarrhythmic action, that is, depression of responsiveness and slowing of conduction.[15,22,23] The dilemma that arises is that these depressant effects of antiarrhythmic agents produce or intensify the very characteristics of abnormal cells that are thought to be conducive to reentry, that is, poor response and slow conduction. The observations that have been cited relating to lidocaine highlight the question: Why should an agent that further retards slowed conduction suppress, rather than promote reentry? It is possible that the antiarrhythmic properties of certain pharmacologic agents are unrelated to their depressant effects on responsiveness and conduction. On the other hand, the depressant effects of such agents could suppress reentrant arrhythmias if they were highly selective. If reentry is usually a consequence of very slow conduction in severely abnormal cells, lidocaine could suppress reentry by extinguishing, not just slowing, propagation in such cells. If the depressant effects of lidocaine on normal or moderately abnormal cells were relatively weak, conduction in such cells would be only slightly affected and the creation of reentry by lidocaine would be unlikely.

The aim of our experiments was to explore these possibilities and extend previous observations by focusing on markedly abnormal cells that could be strongly implicated in the generation of arrhythmias. To this end, we produced abnormal cells by two methods, recognizing that each method presents uncertainties with respect to the reproducibility of the experimental conditions in diseased hearts in vivo. It is arguable that hypoxia in vitro is not exactly comparable with simple hypoxia with adequate blood flow in vivo. The blood flow in vivo might mitigate changes in the extracell milieu during anaerobic metabolism more effectively than the combination of diffusion and superfusion in vitro. Thus hypoxia in vitro may mimic ischemia in vivo. Because hypoxia itself is not the focus of our interest, this possible adulteration of hypoxic with ischemic conditions is not necessarily unwelcome. In the experiments with ischemic epicardium, the superficial cells were exposed to physiologic solution with a high PO_2. Therefore, they were not "ischemic" during the period of study. Because the electrophysiologic abnormalities of these cells changed little during the course of several hours of superfusion, it is not improbable that similar abnormalities existed in vivo. The abnormalities must have been the result of relatively stable alterations in intracell composition or in sarcolemmal structure or function produced by the preexisting ischemia.

Lidocaine effect on propagated activity in ischemic or hypoxic myocardial cells: The observation in our studies that appears most significant in relation to the antiarrhythmic action of lidocaine was the drug's extinguishment of propagated activity in myocardial cells *severely* affected by ischemia or hypoxia and its relatively small effect on normal or mildly abnormal cells. We found no evidence of anomalous automaticity in myocardial cells of the epicardial or endocardial preparations in the form of diastolic depolarization, after-depolarizations or incomplete repolarization.[24] Purkinje fibers of the endocardial preparations were affected only minimally; they did not show enhanced diastolic depolarization. This failure to observe any examples of abnormal automaticity gains significance against a background of more than 300 separate impalements in these preparations. On the other hand, conduction in myocardial cells was invariably greatly slowed and irregular in both types of preparations when abnormal spontaneous beats occurred. We infer that the mechanism for the spontaneous beats in these preparations was reentry involving myocardial cells.

Reentry and unidirectional versus bidirectional block: Many people have postulated that antiarrhythmic agents might abolish reentry by converting "unidirectional" block to "bidirectional" block. This terminology is more appropriate for unidimensional models of conduction, such as strands or rings, than for propagation on planar surfaces (as in our preparations), or within volumes of tissue. The terminology has the added drawback of implying that the critical determinants of success in propagation are spatial, whereas they may be temporal. At the site of unidirectional block, the impulses arriving from different directions also arrive at different times. Models of reentry generally represent

an *earlier* impulse blocking at a site of unidirectional block with a *later* impulse (arriving by way of a slowly conducting pathway) successfully traversing the site and reentering. The crucial factor may not be the direction of the approach of the impulse but the time allowed for recovery at the site of unidirectional block. Nevertheless, our observations constitute a validation of the old postulate because "extinguishment of conduction" in our terminology may be equated with "bidirectional block" in the other terminology.

Lidocaine and potassium-depolarized cells: The studies on potassium-depolarized cells by Chen et al.[11] allowed more controlled and quantitative assessment of the effects of lidocaine than our own studies, which were designed to more closely correspond with clinical conditions. They provide information that may be pertinent in explaining our observations of extinguishment of propagated responses in abnormal cells as opposed to the mere depression of responses noted in other studies.[2,13,18,19] In the potassium-depolarized cells, Chen et al.[11] observed that lidocaine-induced depression of responsiveness was greater the more the cells were depolarized; that is, the relation between $\dot{V}$max and membrane potential was more steep after lidocaine[11]. This observation encourages the prediction that the depressant effect of lidocaine on very abnormal cells might be so great that severely depressed responses could be abolished. Unfortunately, it was not possible to verify this prediction in the potassium-depolarized, but otherwise normal, cardiac cells studied by Chen et al.[11] The lower limits of the responsiveness curve, that is the lowest values of $\dot{V}$max observed, remained unchanged by lidocaine. In other words, there were just as poor responses with lidocaine as without, but with lidocaine the poor responses were generated at more positive levels of membrane potential. Perhaps the inability to demonstrate abolition of very poor responses by lidocaine was due to the apparent absence of exceedingly poor responses in the potassium-depolarized but otherwise normal cells. The conduction velocities were not presented, but the lowest values of $\dot{V}$max illustrated were in the range of 25 to 50 v/sec, values that might not be associated with "very slow conduction"[25] or a propensity for reentry. In contrast, in our hypoxic and ischemic cells, values of $\dot{V}$max below 20 v/sec were commonly observed. It was clear that propagation was very slow in some regions as evidenced by very delayed activation times.

Similarly, in previous reports of the depressant effects of lidocaine on abnormal cells, the abnormalities may not have been as severe as in our preparations. In the studies of Hondeghem et al.,[12] membrane responsiveness of cardiac cells moderately depressed by hypoxia was further depressed by lidocaine. Kuppersmith et al.[13] showed that lidocaine delayed activation time in ischemic myocardium by about 20 percent. It appears (Ref. 13, Fig. 1) that conduction was not greatly delayed by ischemia at the time that lidocaine was administered in those studies. There was no indication of spontaneous ectopic beats at the time of administration of the agent. Neither report documented abnormal spontaneous beats due to lidocaine-induced worsening of slowed conduction, such as that we observed on one occasion (Fig. 5).

In addition to depressing steady-state responsiveness, lidocaine has been shown to delay recovery of responsiveness in potassium-depolarized cells.[11] This effect is also selective in that it is proportional to the degree of potassium-induced depolarization. It is axiomatic that prolongation of refractoriness protects against generation of reentrant ectopic beats.[26] The ability to prolong refractoriness has been considered an important characteristic of antiarrhythmic agents. Lidocaine was thought to be anomalous because it shortened both the action potential and the refractory period of normal cardiac cells. It appears now that lidocaine does indeed prolong refractoriness in an absolute sense in abnormal cells by delaying recovery of responsiveness and recovery of excitability well beyond the completion of repolarization. Prolongation of refractoriness by this mechanism may be much greater than prolongation produced by agents that primarily affect action potential duration. From the time constants reported by Chen et al.[11] and some of our recordings, it is apparent that recovery of responsiveness in very abnormal cells may be delayed by lidocaine for seconds. In our studies, there were no observations to support the contention that lidocaine owes it antiarrhythmic action to improvement of responsiveness and conduction in depressed cells.[3,15]

Hypothesis for antiarrhythmic action of lidocaine: The observation of the effects of lidocaine on potassium-depolarized cells and on hypoxic and ischemic cells generating arrhythmias encourage formulation of a selectivity hypothesis for the antiarrhythmic action of lidocaine. We propose that lidocaine owes its antiarrhythmic potency to the abolition of markedly depressed responses and extinguishment of very slow conduction. It is likely that this extinguishment results not only from the drug's effects on steady-state responsiveness, but also from its marked prolongation of recovery time and marked reduction of excitability (Fig. 4) in severely abnormal cells. The added depression of lidocaine of normal or moderately abnormal cells is an undesirable factor in the antiarrhythmic effect because it may occasionally induce reentry. In other words, the antiarrhythmic potency of the agent is not directly related to a shift in the membrane responsiveness curve but to ablation of the lowest portion of the curve, that is, the lowest values of $\dot{V}$max. Because diseased hearts must contain a spectrum of abnormal cells, ranging from severely depressed to only slightly depressed, it must be postulated that successful reentry circuits usually include severely depressed cells that would be rendered quiescent by lidocaine. On the other hand, the population of less abnormal cells must retain sufficiently rapid conduction even after added depression by lidocaine that reentry is unlikely. The ideal antiarrhythmic agent would completely suppress responses in severely abnormal cells without affecting normal or mildly abnormal cells.

Fast and slow channel conduction in generation of reentrant arrhythmias: Recently, it has been proposed that very slow conduction and reentrant arrhythmias may be, primarily or exclusively, manifestations of cells operating at resting potentials more positive than −55 mv.[27] It was suggested that above this level of membrane potential, the fast channel is inactivated; "slow responses" with very slow upstrokes result from slow current through the slow channel. However, in our preparations, very slow conduction and reentry appeared to depend on poor action potentials that were inhibited, not only by lidocaine, but by tetrodotoxin, a specific blocker of the fast channel.[28,29] Moreover, there

were indications that in *abnormal* cells, the fast channel may be depressed by factors in addition to the loss of membrane potential. Therefore, the voltage-dependent properties of the fast and slow channels of normal cardiac cells may not be sufficient to explain the behavior of abnormal cells. Our observations, considered in the light of the clinical efficacy of lidocaine in ischemic ventricular arrhythmias, suggest that abnormal depression of the fast channel may be an important factor in the generation of reentrant arrhythmias in ischemic heart disease. The specific factors and mechanisms by which the fast channel may be depressed, independent of the level of membrane potential, remain to be elucidated.

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Effect of Propranolol on Mitochondrial Morphology During Acute Myocardial Ischemia

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The analysis of drug-induced alterations on the early ultrastructural changes of acutely ischemic myocardium may offer clues to mechanisms of action by which interventions such as propranolol reduce infarct size after coronary occlusion. The left main coronary artery was occluded in 27 rats; in 13 rats propranolol (20 mg/kg intraperitoneally) was administered 10 minutes before occlusion; 14 untreated rats served as controls. Three hours after occlusion samples for electron microscopy were taken from four sites, three ischemic and one nonischemic, of the left ventricle. Morphometric study of 1 μ thick sections of ischemic samples showed that 84 $\pm$ 5 percent (mean $\pm$ standard error of the mean) of myocardial cells and 61 $\pm$ 4 percent of vessels were damaged in untreated controls compared with 42 $\pm$ 6 percent ($P < 0.001$) of myocardial cells and 27 $\pm$ 5 percent ($P < 0.001$) of vessels in propranolol-treated rats. Morphometric study of electron micrographs demonstrated that in the injured myocardial cells there were no significant differences in incidence or degree of nuclear, glycogen, sarcoplasmic reticular and myofilament changes between the two groups. However, in injured cells, mitochondrial swelling was distinctly less in propranolol-treated than in untreated rats. Thus, propranolol reduces or delays the damage to both the myocardial cells and the vessels. Moreover, its effect is maximal in protecting the mitochondria, thereby suggesting that mitochondrial salvage may play a role in propranolol's ability to protect ischemic myocardium.

Although several interventions have been shown to decrease the size of experimental myocardial infarction,[1–4] the mechanism of their salutory effects is not clear. Study of how such interventions affect the cardiac ultrastructure in acute ischemia may offer insight into their mode of action. Specifically, electron microscopic techniques permit determination of whether an intervention changes the early morphologic sequence of events after coronary occlusion and whether it protects some organelles preferentially. This study was carried out to investigate the effect of propranolol, a drug that has been shown to decrease experimental myocardial infarct size,[1,5–8] on ultrastructural changes that occur during the early phase of acute myocardial ischemia in the rat.

Methods

Experimental procedure: The study was carried out in albino Sprague-Dawley rats (Charles River Breeding Laboratory) weighing approximately 250 to 300 g, in which the left main coronary artery was occluded. This model of coronary occlusion was described previously.[9] Briefly, in rats anesthetized with ether left thoracotomy was performed, the heart was everted from the thoracic cavity and the left coronary artery was occluded about 2 to 3 mm from its origin with 4-0 silk suture on an atraumatic needle. The heart was repositioned inside the thorax and the chest closed with a purse string suture. Thirteen rats were pretreated with propranolol (20 mg/kg body weight intraperitoneally, 10 minutes before occlusion), and 14 rats remained untreated. Two additional rats were

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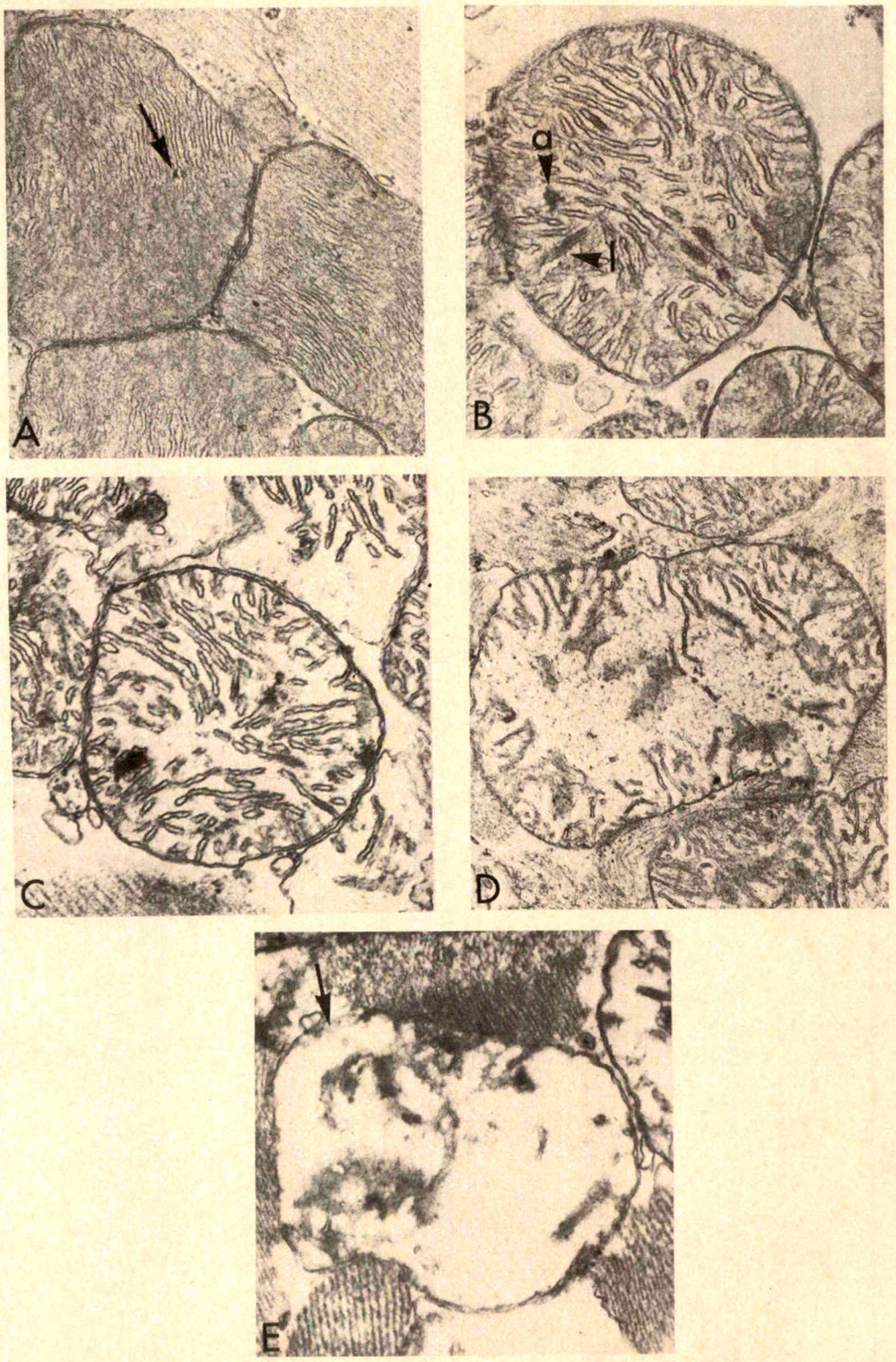


FIGURE 1. Electron micrographs of rat mitochondria. **A,** normal mitochondria from nonischemic myocardium showing tightly packed cristae and grey matrix density. A few small normal granular densities are present **(arrow).** Mitochondria with these morphologic features received a grade of 0. (×35,000, reduced by 14 percent.) **B** to **E,** mitochondria from ischemic rat myocardium after 3 hours of coronary occlusion. **B,** mitochondria showing early evidence of damage. There is early clearing of the matrix density and separation of the cristae. A large amorphous matrix density (a) and a linear density (l) are present. Mitochondria with these morphologic features received a grade of 1. (×37,000, reduced by 16 percent.) **C,** mitochondria from ischemic myocardium showing greater evidence of swelling as manifested by further clearing of matrix density and separation of cristae. Mitochondria showing these morphologic features were graded 2. (×40,000, reduced by 16 percent.) **D,** mitochondria from ischemic myocardium showing massive swelling and disruption of cristae. Such mitochondria received a grade of 3. (×35,000, reduced by 16 percent.) **E,** mitochondria from ischemic myocardium showing marked swelling and rupture of inner and outer mitochondrial membranes **(arrow).** Such mitochondria received a grade of 4. (×36,000, reduced by 16 percent.)

subjected to a sham operation in which the stitch under the coronary artery was not tied. Three hours after occlusion, the animals were reanesthetized and their heart excised. Just before excision, carbon black (1 mg/kg) was injected intravenously to determine (1) whether the coronary artery was successfully occluded, and (2) to distinguish perfused tissue (black areas) from nonperfused tissue (pink areas).

Tissue samples: Transmural sections for electron microscopy were obtained from both the perfused mid ventricular septum (black area) and from three sites on the nonperfused anterior ventricular wall (pink areas). The epicardium and endocardium were trimmed from the muscle. Tissue from each site was cut into six or seven transmural 1 to 2 mm thick slices under cold 1 percent osmic acid and fixed for 1 hour in the osmic acid. The tissue samples from each of the four sites were then dehydrated in graded alcohol, passed through propylene oxide and a 1:1 mixture of propylene oxide plus Epon 812 overnight. Two samples from each of the four sites were randomly chosen and embedded in Epon 812. This procedure ensured complete randomization. Sections approximately 1 μ thick (that is, thick sections) were stained with toluidine blue for light microscopy. Thin sections were mounted on plain copper grids and stained with aqueous uranyl acetate and lead citrate and examined on a Philips 201 electron microscope.

Grading of ischemic damage: The groups were compared quantitatively using both thick and thin sections. To estimate the overall percent of injured myocardial and endothelial cells in ischemic tissue, a point counting technique was used. This entailed examining 1 μ thick sections with light microscopy, at a magnification of ×400, under a grid.[10] If a point on the grid fell on a myocardial cell, the morphologic severity of the ischemic damage was graded using the following criteria:

0 = normal myocardial cell.
1 = nuclear chromatin clumping alone, or with occasional vacuoles, plus myocardial relaxation as manifested by I bands.
2 = the findings in 1, plus intermyofibrillar edema and more vacuoles.
3 = the findings in 2, plus numerous vacuoles or the sarcolemmal membrane lifted off the myofibrils, or both.
4 = severe swelling and architectural disruption.

When each point falling on a myocardial cell was assigned a numerical value of 0 to 4, a distribution of severity of ischemic damage per section was determined. A mean ischemic score ($\bar{I}$) was determined for each rat by calculating the average severity (0 to 4) of myocardial cell injury from the three ischemic sites per rat. When morphometry was carried out in this manner, approximately 600 cells per rat were graded. Vessels were recorded as being normal or having ischemic changes, including intraluminal blebs, fibrin deposits, red blood cell stasis and localized hemorrhage.

Morphometric analysis of electron micrographs: For more detailed analysis of organelle changes in the myocardial cells, electron micrographs (magnification ×7,000 to 15,000) were examined morphometrically under a grid. To verify whether propranolol preferentially protected mitochondria, overall myocardial cell injury was ranked independently of mitochrondrial structure from 0 to 4 as follows:

0 = normal (other than mitochondrial change).
1 = minimal ischemic changes (nuclear chromatin clumping and margination, I bands, glycogen loss).
2 = moderate ischemic changes (the findings in 1, plus early intermyofibrillar and sarcoplasmic reticular edema).
3 = severe ischemic changes (findings in 2, plus subsarcolemmal blebs, sarcolemmal gaps and marked edema).
4 = total architectural disruption (with loss of sarcomere structure and absent sarcolemmal membrane).

The severity of mitochondrial swelling (Fig. 1) was graded 0 to 4 as follows:

0 = normal mitochondria.
1 = early swelling as manifested by clearing of matrix density and separation of cristae.
2 = more marked swelling as manifested by further clearing of matrix density and separation of cristae.
3 = massive swelling with disruption of cristae.
4 = massive swelling with disruption of cristae and rupture of inner and outer mitochondrial membranes.

When a point on the grid fell on a mitochondrion, this mitochondrion was assigned a numerical value of 0 to 4, depending on its morphologic degree of damage. A mean mitochondrial grade for each cell was obtained by calculating the weighted average (0 to 4) of mitochondrial swelling. Approximately 50 cells per rat and 750 to 1,000 mitochondria per rat were graded in this manner.

The degree of sarcoplasmic reticular swelling and myofilament disruption was graded 0 to 3 (0 = absent, 3 = severely altered and 1 and 2 = intermediate); the presence of glycogen and lipid was ranked as 0 to 3 (0 = absent, 1 = sparse, 2 = moderately abundant and 3 = more abundant). All slides and electron micrographs were graded without examiners' knowledge of whether they were from untreated or treated rats.

Results

Qualitative: Morphologic appearance of myocardial tissue from sham-operated rats and the nonischemic mid ventricular septum (which was always perfused with carbon black) of rats with coronary occlusion showed normal myocardial cells and normal microvasculature in both untreated and treated groups.

After 3 hours of ischemia, tissue from the anterior ventricular wall (not perfused by carbon black and therefore pink) of untreated rats showed nuclear chromatin clumping and margination, wide I bands, occasional contraction bands, mitochondrial swelling with both amorphous and linear intramitochondrial dense bodies, swollen sarcoplasmic reticulum and scarce or absent glycogen. Amorphous and linear intramitochondrial densities were most prominent in mitochondria that showed minimal to moderate swelling and often were absent in mitochondria that were massively swollen and had disrupted cristae. Lipid accumulation was more marked in those cells that appeared only slightly injured. The microvasculature demonstrated endothelial clearing, blebbing, gaps and scarcity of pinocytotic vesicles; red cell sludging and occasional intraluminal or extravascular fibrin deposits; microscopic foci of hemorrhage, and platelet thrombi.

In the propranolol-treated group, fewer cells appeared damaged in the nonperfused areas. Cells that did

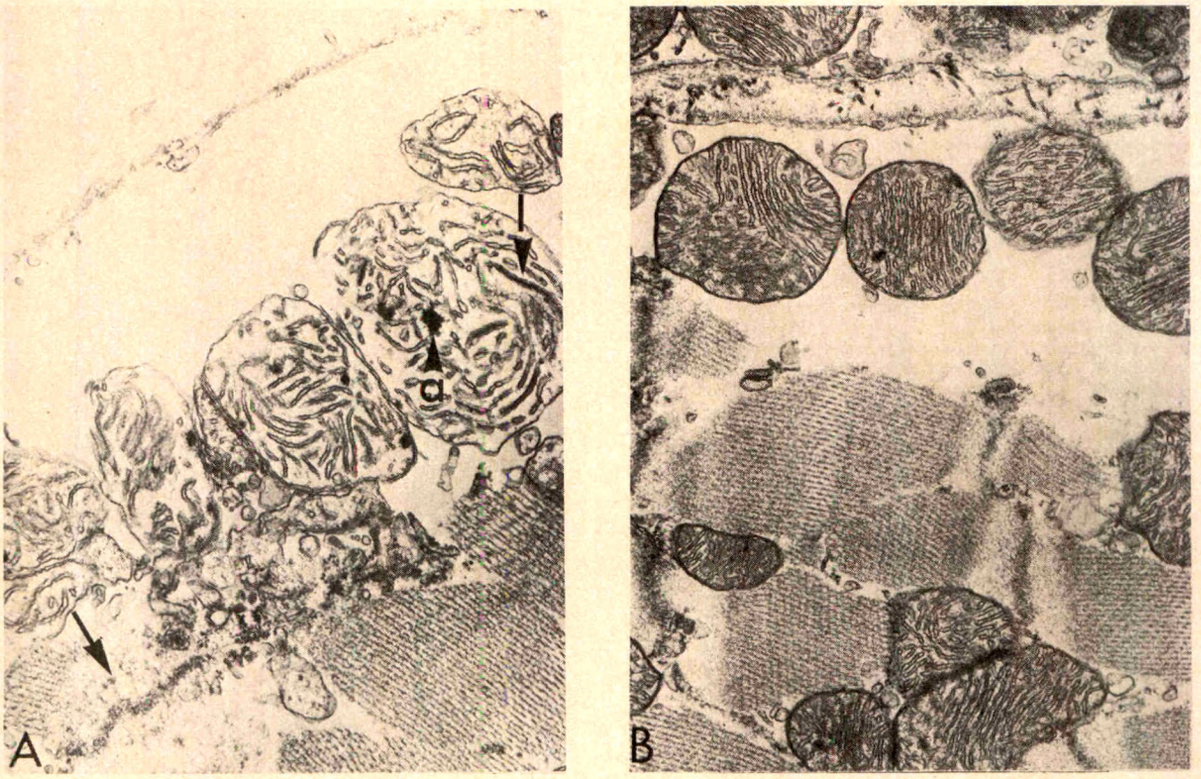


FIGURE 2. Control versus propranolol-treated rat. **A,** ischemic myocardium after 3 hours of coronary occlusion in an untreated rat. The sarcolemmal membrane is lifted off of the myofilaments, forming an edema-filled intracell space. A wide I band **(arrow)** is present and glycogen is sparse. The mitochondria are markedly swollen with clearing of their matrix space, separation of cristae and loss of membrane integrity. Amorphous (a) and linear (l) intramitochondrial densities are present. (×11,000, reduced by 10 percent.) **B,** a markedly damaged region of ischemic myocardium after 3 hours of coronary occlusion in a propranolol-treated rat. The sarcolemmal membrane is again lifted off the myofilaments and wide I bands are present. Mitochondrial swelling is less marked than in the untreated rat. (×20,000, reduced by 10 percent.)

appear damaged had less cell swelling and fewer vacuoles as assessed with light microscopy of 1 μ sections and, in most rats, had less swollen mitochondria as assessed with electron microscopy (Fig. 2). Other than these findings, glycogen loss, nuclear change, sarcoplasmic reticular swelling, myofilament disruption and lipid accumulation were similar in those cells that showed all degrees of ischemic injury.

Quantitative: Results of morphometric analysis of 1 μ thick sections are shown in Table I. In untreated rats, 84 ± 5 percent of myocytes and 61 ± 4 percent of vessels from the unperfused area showed ischemic damage, compared with 42 ± 6 percent of myocytes (P <0.001) and 27 ± 5 percent (P <0.001) of vessels in propranolol-treated rats. The ischemic score from the unperfused area was 1.5 ± 0.1 (mean ± standard error of the mean) in untreated and 0.5 ± 0.1 (P <0.001) in propranolol-treated rats. Thus, in the propranolol-treated rats the damage was both less frequent and less severe.

TABLE I

Morphometric Analysis of 1 μ Sections*

	Myocardial Cells Showing Ischemic Change (%)					Total Cells Showing Damage (%)	Mean Myocardial Ischemic Score (Ī)	Vessels Showing Damage (%)
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4			
Untreated rats	16 ± 5	42 ± 4	22 ± 3	18 ± 2	2 ± 1	84 ± 5	1.5 ± 0.1	61 ± 4
Propranolol-treated rats	58 ± 6	34 ± 4	4 ± 1	4 ± 1	0	42 ± 6	0.5 ± 0.1	27 ± 5
P	<0.001	NS	<0.001	<0.001	0.05 < P <0.1	<0.001	<0.001	<0.001

* This analysis is only of specimens from the nonperfused zone.
Grade indicates grade of ischemic damage (see Methods for explanation); NS = not significant; P = probability.

TABLE II

Mitochondrial Changes in Ischemic Myocytes

	Mean Mitochondrial Grade*				Number of Amorphous Bodies/Mitochondrion			
	Cell Grade 0	Cell Grade 1	Cell Grade 2	Cell Grades 3 and 4	Cell Grade 0	Cell Grade 1	Cell Grade 2	Cell Grades 3 and 4
Untreated rats	0.4 ± 0.1 (no. = 6)	1.1 ± 0.2 (no. = 12)	1.7 ± 0.04 (no. = 13)	1.8 ± 0.2 (no. = 12)	0.86 ± 0.36 (no. = 6)	0.82 ± 0.26 (no. = 12)	1.36 ± 0.30 (no. = 13)	0.88 ± 0.23 (no. = 12)
Propranolol-treated rats	0.04 ± 0.04 (no. = 7)	0.5 ± 0.2 (no. = 9)	0.7 ± 0.2 (no. = 10)	0.5 ± 0.1 (no. = 9)	0.01 ± 0.01 (no. = 7)	0.83 ± 0.21 (no. = 9)	1.17 ± 0.26 (no. = 10)	1.13 ± 0.28 (no. = 9)
P	<0.25	<0.05	<0.001	<0.001	<0.05	NS	NS	NS

* Grade 0 = cells appearing normal except for mitochondrial change; Grade 1 = cells with minimal injury; Grade 2 = moderately injured cells; Grades 3 and 4 = severely injured cells and cells with total architectural disruption. Because there were few cells with total architectural disruption (loss of sarcomere structure and absent sarcolemmal membrane), these were included with the severely injured cells.

no. = number of rats showing a given myocardial cell type; NS = not significant; *P* = probability.

TABLE III

Mean Score of Glycogen, Sarcoplasmic Reticulum, Myofilaments and Lipid Accumulation (0 to 3) From Ischemic Myocytes

	Glycogen Presence	Sarcoplasmic Reticular Swelling	Myofilament Disruption	Lipid Accumulation
Untreated	0.4 ± 0.1	1.3 ± 0.2	1.4 ± 0.1	0.7 ± 0.2
Propranolol-treated	0.8 ± 0.3	1.0 ± 0.2	1.1 ± 0.1	0.7 ± 0.1
P	NS	NS	NS	NS

NS = not significant.

Results of morphometric analysis of electron micrographs are presented in Tables II and III. Mitochondrial swelling occurred less frequently in the propranolol-treated rats than in the control rats in myocardial cells with all degrees of morphologic injury (Table II). The number of amorphous bodies per mitochondrion was similar in both groups except for myocytes that, independent of mitochondrial structure, looked uninjured. In the latter, there were fewer intramitochondrial dense bodies in propranolol-treated rats than in untreated rats. The percent of injured cells that showed intramitochondrial linear densities was similar in untreated (22 ± 6 percent) and propranolol-treated (16 ± 5 percent) rats (difference not significant).

Mean weighted scores (0 to 3) for the presence of glycogen, sarcoplasmic reticular swelling, myofilament disruption and lipid accumulation were similarly calculated (Table III): There was no difference in these scores between untreated and with propranolol-treated animals in ischemically injured cells.

Discussion

Effect of propranolol on ischemic myocardial damage: Propranolol has been shown by electrocardiographic,[1,7] creatine kinase (CK)[1] and histologic analysis[3,5] to decrease ischemic myocardial cell damage after experimental coronary arterial occlusion. Recently, to determine whether propranolol merely delayed or actually prevented necrosis, the volume of myocardial infarcts and that of the preserved myocardium were directly measured both 2 days and 3 weeks after coronary arterial occlusion in untreated and propranolol-treated rats.[6] The volume of the preserved myocardium was measured from total left ventricular CK activity and with planimetry of serially stained histologic sections. Propranolol salvaged a significant amount of the left ventricle not only when its effect was assessed 2 days after coronary occlusion, but also when infarct size was assessed 3 weeks after occlusion. Hence, propranolol did not simply delay necrosis but actually reduced the ultimate amount of necrosis. Furthermore, propranolol has been shown to decrease electrocardiographic evidence of myocardial cell damage in patients[11] and to improve the metabolic indexes of ischemic dysfunction.[12] The mechanism by which propranolol exerts its protective effect is still unknown, although several hypotheses have been suggested. One is that by decreasing oxygen demand, propranolol preserves myocardial tissue in the face of decreased oxygen supply.[1] The relative influence of the reductions in contractility and in heart rate are not well established. Previous studies[1] suggest that propranolol's mechanism of action may not be due to decreasing heart rate alone: When the drug was given to dogs with a coronary occlusion and heart rate was maintained with electric atrial pacing, a marked reduction in S-T segment elevation still occurred.

Propranolol's ability to decrease myocardial oxygen consumption may not be due to beta blockade alone. Recently a dimethyl quaternary derivative of propranolol, which lacks beta adrenergic antagonist properties, was shown to decrease myocardial infarct size after coronary occlusion in the dog.[13] Its mechanism of action is presumably a reduction in heart rate and

myocardial contractility; both actions tend to reduce myocardial oxygen demand. In a recent study by Obeid et al.,[14] propranolol was found to preserve adenosine triphosphate (ATP) in ischemic myocardium, suggesting that oxygen demand may have been reduced.

Another hypothesis is that propranolol stabilizes membranes and thereby decreases lysosomal breakdown and myocardial swelling.[15] However, when d-propranolol (the isomer that has a membrane-stabilizing effect but little beta adrenergic blocking activity) was given to dogs with coronary occlusion, there was no sparing of myocardial tissue.[15] Hence propranolol's effect is probably not due to membrane stabilization alone.

Role of ischemic microvascular injury: A controversial hypothesis is that propranolol improves oxygen supply by increasing coronary collateral blood flow. Although some studies[16–18] have shown an improvement in collateral flow to ischemic myocardium, others[19] have failed to show this or have actually shown a decrease in coronary collateral flow. It is known that propranolol protects both the ischemic myocardial cell and the ischemic microvasculature in the dog.[20] However, the importance of the role that microvascular injury plays in myocardial injury is not well established. Beta adrenergic blockade with propranolol reduces glycogenolysis and lipolysis,[21] but the role of these metabolic changes in sparing myocardial tissue is unknown. A final possibility is that propranolol's mechanism of action is related to the drug's ability to shift the oxygen-hemoglobin dissociation curve to the right,[22] an action that would favor the oxygenation of ischemic tissue.

Propranolol's effect on mitochondrial structure: Our study showed that propranolol decreased both myocardial cell injury and microvascular injury during the early stages of acute myocardial ischemia. Light microscopy of 1 μ sections revealed fewer swollen cells with less vacuolization, intermyofibrillar edema and subsarcolemmal blebs in propranolol-treated rats: Electron microscopic studies showed that propranolol appeared to exert an even more profound effect on reducing mitochondrial swelling.

It is clear from the heterogeneity of cell types (grade 0 to 4) in our study that not all myocardial cells die simultaneously. Some show no or minimal damage (grade 0); others show marked damage (grade 4). Because propranolol delays and prevents ischemic damage, one would expect the sequence of mitochondrial changes to be delayed in the treated group. This occurred, as expected. The unexpected finding of our study was that in cells having similar morphologic damage independent of mitochondrial structure, there was less mitochondrial damage in propranolol-treated than in untreated rats. In other words, mitochondrial structure was preserved by propranolol out of proportion to the rest of the cell structure. This raises the possibility that protection of mitochondrial integrity may play a role in preservation of ischemic myocardium by propranolol. Jennings and Ganote[23] showed that mitochondria isolated from ischemic dog myocardium after 60 minutes of coronary occlusion have marked functional and morphologic abnormalities. Thus, these organelles are very sensitive to ischemic damage, and it has been proposed that mitochondrial damage may play an important role in the pathogenesis of irreversible injury.[23] The mechanism by which propranolol preferentially preserves mitochondrial integrity is unclear. It may be speculated that it is related to propranolol's ability to reduce myocardial oxygen demand. If the myocardial cell's need for oxygen were reduced during ischemia, the mitochondria (the chief supplier of ATP for the cell) would be expected to exhibit fewer morphologic abnormalities. Moreover, the recent findings that propranolol preserves ATP stores in ischemic myocardium[14] supports the idea that mitochondrial salvage occurred. Although propranolol has been shown to decrease mitochondrial respiration in vitro by inhibiting the reduced form of nicotine adenine dinucleotide (NADH) oxidase,[24] it is unclear whether it is this effect that results in mitochondrial preservation during ischemia. Our study demonstrates that an intervention can exert preferential protection of a specific organelle, namely, the mitochondria. In contrast, hyaluronidase, which also decreased the number of myocardial cells and vessels with ischemic damage, did not show any specificity to protect certain organelles but did result in an increase in cytoplasmic glycogen.[25]

The reason that the number of amorphous and linear densities per mitochondrion was not similarly decreased by propranolol is unclear. If propranolol decreased mitochondrial swelling, one marker of mitochondrial injury, then the number of intramitochondrial densities, presumably another marker of mitochondrial injury, might also be expected to decrease. However, we observed no correlation between the degree of swelling and number of dense bodies per mitochondrion. In fact, mitochondrial dense bodies were present more frequently in mitochondria that were less swollen and were seldom seen in mitochondria that were massively swollen with disrupted cristae. Amorphous intramitochondrial dense bodies occur at approximately the same time that irreversible injury to ischemic myocytes occurs,[26] but a causal relation has not been proved. Their exact chemical makeup and functional significance remain unclear.

In conclusion, propranolol was shown to alter the early ultrastructural events of acute myocardial ischemia, protecting both the ischemic myocardial cell and the ischemic microvasculature. Propranolol appeared preferentially to decrease mitochondrial swelling, a finding that suggests that mitochondrial salvage may play a role in propranolol's ability to protect ischemic myocardium.

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Techniques for Right and Left Ventricular Endomyocardial Biopsy

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Right ventricular endomyocardial biopsy using percutaneous right internal jugular approach proved a safe and easily performed technique in more than 1,300 procedures. Adequate tissue was obtained in more than 98 percent of patients and morbidity rate was remarkably low. Other approaches to the right ventricle may be used, but retrograde left ventricular endomyocardial biopsy appears to be the safest and most reliable alternative to transjugular right ventricular biopsy. The safety and success of the techniques for right and left heart biopsy described depend on meticulous attention to methodologic detail.

Right and left ventricular myocardial biopsy using the transvascular intracardiac approach has proved, since its introduction in 1962,[1] to be a surprisingly safe method.[2,3] We have performed at Stanford University Medical Center more than 1,300 right ventricular biopsy procedures yielding more than 4,200 separate endomyocardial biopsy specimens, without a fatality.[4] The most serious complication, cardiac tamponade, occurred in only four patients, and the incidence rate of any complication was less than 1 percent. Although our experience with left ventricular biopsy is much less extensive (70 cases, 161 specimens, no complications), we have modified previously described techniques[5,6] to ensure safety and simplicity. Although cardiac biopsy finds its greatest application in our cardiac transplantation program and as a tool for research, we recognized a number of additional clinical applications (Table I).

Because the procedure is performed in only a few centers in the United States and abroad, this paper is offered as a detailed description of what we consider to be the optimal methods, on the basis of safety, ease and tissue yield, for nonsurgical biopsy of the beating human heart. It is our intention to describe the technique of myocardial biopsy rather than to present any detailed summary of results.

Right Ventricular Endomyocardial Biopsy

Procedure

Bioptome: The Stanford right ventricular endomycardial bioptome was originally a modification of the Konno bioptome,[7,8] and has undergone continued modification. It is a catheter 50 cm in length with a 9.0F outer diameter. A surgical forceps on the proximal end has been affixed to a movable wire within the catheter shaft to permit opening and closing of a pair of jaws at the distal end (Fig. 1). The bioptome is introduced into the venous system with a modification of the Seldinger percutaneous technique. The materials required for right heart biopsy, in addition to the bioptome and the standard equipment used for percutaneous right heart catheterization, are listed in Table II.

Cannulation of jugular vein: For 8 hours before the procedure the patient is given nothing by mouth except liquids. Premedication is usually not required. During the procedure the patient lies supine on the catheterization table. A stable, reliable electrocardiogram must be monitored continuously. The skin of the right side of the patient's neck is rendered sterile in the usual manner. The aperture of a large sterile drape is placed over the catheter insertion site and a tent is formed by supporting one end of the drape over a supporting bar fixed

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TABLE I

Indications for Heart Biopsy at Stanford Medical Center

Suspected cardiac homograft rejection
Suspected myocarditis
To prove the presence of primary cardiomyopathy
Suspected drug or chemical-induced myocardiopathy
Suspected secondary cardiomyopathy (especially amyloidosis, sarcoidosis, and hemochromatosis)
Suspected endomyocardial fibrosis
To detect and quantify the severity of adriamycin-induced cardiotoxicity
To differentiate between constrictive pericardial disease and restrictive myocardial disease
Suspected small vessel coronary arteriopathy
Research applications

to the end of the table to allow the patient to breathe comfortably. The proper site for percutaneous puncture of the right internal jugular vein is identified in the following manner: The patient is asked to turn his head as far as possible to his left. The medial and lateral divisions of the sternocleidomastoid muscle are then located by palpation. If they are difficult to feel, the patient is asked to lift his head from the table with his head still turned to the left. This maneuver will tense the muscles and make them more readily palpated. The medial belly of the muscle originates from the manubrium just below the suprasternal notch. The lateral belly separates from the medial belly approximately 8 cm above the clavicle and attaches to the clavicle 1 to 4 cm lateral to the origin of the medial division. The puncture site is located directly between the two divisions of the sternocleidomastoid muscle 3 cm above the superior border of the clavicle. The lateral belly of the muscle is smaller than the medial but can usually be identified. In about 5 percent of patients the lateral muscle cannot be seen or palpated, and in these patients the medial belly tends to be large. In these instances a puncture site should be selected as close as possible to the lateral edge of the single belly, again 3 cm above the clavicle.

The skin over the site is anesthetized with a small volume of local anesthetic agent. Care is taken at this point to infiltrate only the skin and shallow subcutaneous tissue because deeper injection might enter the carotid sheath and cause partial tamponade of the internal jugular vein, making it difficult or impossible to locate. In addition, we have noted that large volumes of anesthetic agent injected in this area can result in temporary paralysis of the right hemidiaphragm or the right vocal cord, or in a right Horner's syndrome. Once a guide wire has been positioned in the vein, additional anesthetic agent can be safely and accurately applied although it is usually unnecessary.

After anesthesia, a 1 cm incision through the skin is made with a no. 11 blade and the tissue is bluntly spread apart with a hemostat. A 1.5 inch (3.81 cm) 22 gauge needle is then advanced to the internal jugular vein through the skin wound. Continuous suction is applied to the needle with a 5 cc syringe while the needle is directed at an angle 30° caudad from the vertical and 20 to 30° toward the patient's right. The needle generally does not have to be advanced beyond 2.5 cm. Frequently the vein is transfixed without blood return, and blood is aspirated into the syringe only during withdrawal of the needle. When the vein is located, the probing needle should be left in the vein and the syringe removed (Fig. 2A). The needle is left in place for two reasons: (1) the probe needle serves as a useful guide for subsequent insertion of the large needle; and (2) removal of the probe needle may be associated with sufficient bleeding into the carotid sheath to again produce tamponade of the vein. If the vein is not found by this approach, the needle should first be angled more laterally, and then medially. The direction of the needle should not be changed when the needle tip is under the skin because arterial laceration might occur. If, on medial angling of the needle, the carotid artery is entered, the needle should be removed and moderate pressure should be held on the artery for 2 minutes; so medial an approach should not be taken again. If the vein is not found after careful probing, and if the entry site is verified to be accurately placed, then the table should be placed in the Trendelenburg position. If this is not possible, probing can be done while the patient performs a Valsalva maneuver. If the vein still cannot be found, an attempt on another day is often successful, especially if the patient is well hydrated. Alternate venous approaches may also be used (see later).

Insertion of sheath and dilator: After the vein is located, a 3 inch (7.62 cm) 18 gauge thin wall needle is advanced with syringe suction into the vein along side the probe needle. Once

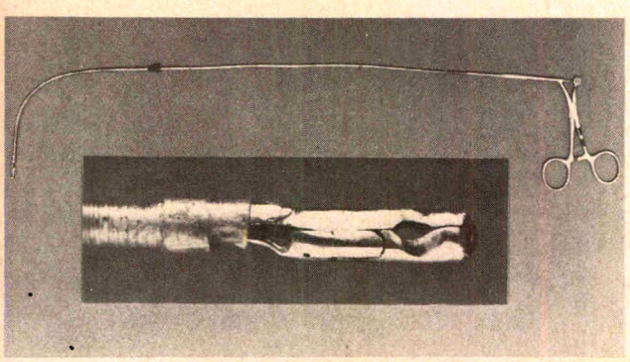


FIGURE 1. The Stanford endomyocardial bioptome is shown with the jaws in a closed position. The handle is modified from a mosquito clamp; the catheter shaft is slightly less than no. 9.0 French in diameter and is 50 cm in length. The inset is a closeup of the bioptome cutting jaws.

TABLE II

Equipment for Right Ventricular Endomyocardial Biopsy*

Large plastic drape, large aperture[a]
Drape support
18 gauge thin-wall needle[b]
No. 9.0 French sheath and introducer[c]
Bioptome[d]
Filter paper[e]
Catheter plug[f]
10 percent formalin
2.5 percent glutaraldehyde
Embedding solution[g]
Isopentane and dry ice
Pericardiocentesis tray

* In addition to the usual material used for right heart catheterization by standard percutaneous techniques.

[a] Steri-Drape®, 3M Co., St. Paul, Minnesota.

[b] Percutaneous entry needle (without baseplate), Cook, Inc., Bloomington, Indiana.

[c] UMI Corporation, Ballston Spa, New York.

[d] no. 9.0 French right ventricular bioptome, Werner P. Schulz, San Bruno, California or Jacobus Scholten, Palo Alto, California.

[e] no. 2 qualitative filter paper, 9.0 cm diameter, Whatman Co., Clifton, New Jersey.

[f] Abbott male adaptor plug, Abbott Laboratories, Chicago, Illinois.

[g] Ames OCT Compound, Ames Co., Elkhart, Indiana.

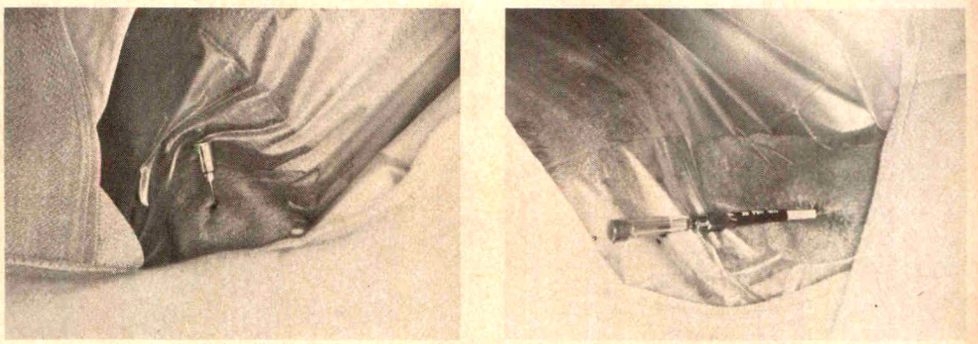


FIGURE 2. Left, the 22 gauge probe needle is positioned in the right internal jugular vein as viewed from the patient's right side looking caudocephalad. The needle enters the skin between the divisions of the sternocleidomastoid muscle 3 cm above the clavicle. To enter the vein the needle was directed slightly caudad and rightward (see text). **Right,** the sheath, as viewed from the patient's right, is inserted in the vein and occluded with a catheter plug. The patient continues to look to his left.

again, blood may be freely aspirated immediately on puncture of the anterior wall of the vein or only upon withdrawal of the needle. When free-flowing blood is obtained, a 0.035 inch (0.89 cm) 40 cm guide wire is inserted into the needle and directed fluoroscopically to the right atrium, followed by removal of the two needles. At this point additional anesthetic can be administered before placing the 9.0 French sheath and dilator into the vein over the guide wire (Fig. 2B). A catheter plug is used to close the hub of the sheath whenever it is not in use.

The patient must be given careful instructions to suspend respirations when the sheath is unplugged or is not occluded by the catheter. This is necessary to avoid air embolism, which will occur in any patient with normal venous pressure if an inspiration is taken while the sheath is open. The patient should not be asked to take a deep breath before the sheath is unplugged because most patients perform a Valsalva maneuver during breath-holding after full inspiration, and this will lead to unnecessary blood loss through the open sheath. The patient can breathe normally while the bioptome is in the sheath, but if a catheter of less than 9.0 French outer diameter is subsequently inserted into the sheath, the sheath should be removed because even a single French size mismatch between catheter and sheath might lead to air embolism. If the patient is unable to cooperate adequately, air embolism can be avoided by performing the procedure in the Trendelenberg position or by fashioning a rubber seal over the sheath through which the bioptome can be passed.

Positioning of bioptome at biopsy site: Our right ventricular endomyocardial bioptome is curved at the distal end, forming a nearly 90° angle (Fig. 1). This angle can be varied between 45° and 90° by changing the tightness of closure of the handle, which greatly improves the maneuverability of the bioptome. The curved distal end of the bioptome lies in the same plane as the handle so that the attitude of the handle indicates the direction of the forceps at the end of the catheter. The bioptome is advanced through the sheath to the lower third of the right atrium with the tip pointing laterally. The catheter is then turned clockwise 180° and advanced across the tricuspid valve. In general, little manipulation is required to negotiate the valve and direct the tip to the right ventricular apex. We make every attempt to obtain specimens from the septum to avoid transmural biopsy of the right ventricular free wall. Thus, as soon as the tricuspid valve is crossed, the tip should be pointed down toward the septum while it is advanced to the apex (Fig. 3). Proper position of the jaws for biopsy is identified by the following characteristics: the occurrence of ventricular premature beats, foreshortened appearance of the curved portion of the catheter on fluoroscopy, location of the tip below the shadow of the diaphragm well past the left border of the spine (Fig. 4), and the sensation of ventricular contractions transmitted to the operator's hands.

Obtaining biopsy specimens: After the bioptome is seated at the biopsy site, it is withdrawn 1 cm and the jaws are opened and readvanced against the myocardium. The handle is promptly closed, which results in closure of the jaws, although they may appear to remain partially open if a large sample is trapped between them. The tissue is separated from the heart with a gentle tug. If a very forceful tug is required, provoking multiple ventricular premature contractions and considerable inward retraction of the ventricular wall, the specimen should be released because pericardial tissue might be included in the bite. This is a rare occurrence.

Two to five specimens are obtained in this manner, depending upon their size and the nature of the studies planned for the tissue. Each specimen is obtained serially by reinsertion of the bioptome. Between insertions the bioptome is

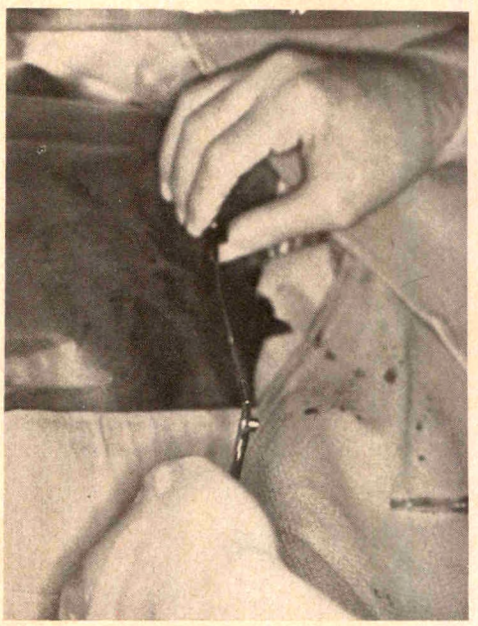


FIGURE 3. Photograph taken from above the patient's head with the camera pointed toward his feet. At **right,** is the patient's right side. The bioptome has been advanced through the sheath across the tricuspid valve. The operator's left hand holds the bioptome handle, which has been *pointed downward* to direct the tip of the bioptome toward the right ventricular septum.

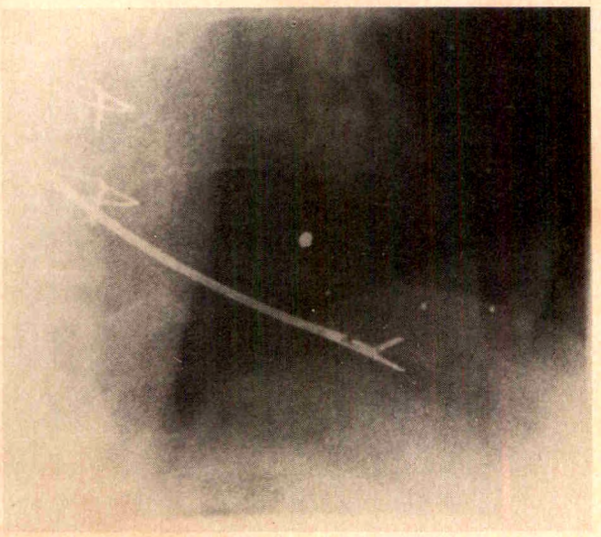


FIGURE 4. Cinefluoroscopic image of the bioptome within the heart. The left lung field is seen as a bright area **at upper right. At left,** sternal suture wires can be seen overlying the shadow of the vertebral column. The bioptome is positioned for biopsy. The distal portion of the instrument crosses the spine and is advanced well beyond its lateral border. The tip of the bioptome is positioned well below the superior border of the diaphragm on fluoroscopy.

meticulously cleaned with sterile saline solution. The process of actually removing the tissue from the heart generally takes only 5 minutes. Each specimen is very gently removed from the jaws of the bioptome (Fig. 5A) and placed on a piece of filter paper wetted with normal saline solution (Fig. 5B). The sample can usually be removed from the bioptome by applying the filter paper to it. If it does not come out easily from the bioptome head, then it should be very gently teased out with a 25 gauge needle. Care should be taken in handling these specimens because artifact is introduced by rough handling. After the specimen is placed on the filter paper it is immediately transferred to the appropriate solution. Great effort should be taken to place the samples in fixative promptly after separation from the heart because mitochondrial degeneration appears in specimens that have remained unfixed for long periods of time.[9]

TABLE III

Complications of Right Ventricular Endomyocardial Biopsy

Cardiac perforation
Right pneumothorax
Air embolism
Atrial arrhythmias
Transient nerve palsies
Right Horner's syndrome
Right recurrent laryngeal nerve paresis
Right phrenic nerve paresis

Complications

The major complication associated with right ventricular biopsy is cardiac perforation with tamponade (Table III). In our series this occurred four times in more than 1,300 procedures. In two patients with this complication a single pericardiocentesis was adequate therapy. One patient required catheter drainage of the pericardium for several hours, and one patient required no therapy. In all four instances, tamponade was heralded by bradycardia followed promptly by hypotension.

The other complications listed in Table III relate to internal jugular vein puncture. These complications are almost always caused by inexperienced operators and are usually due to unfamiliarity with or inaccurate identification of the anatomic landmarks.

When internal jugular puncture was successful, we obtained adequate tissue in 98 percent of procedures. The presence of right ventricular apical clot was the usual cause for inadequate tissue yield.

Tissue Preservation

One piece of tissue is preserved in 10 percent buffered formalin for subsequent light microscopy. When cardiomyopathy is the suspected diagnosis (which is the case in the majority of our patients, apart from transplant recipients), serial cuts of the formalin-preserved specimen are made for staining with hematoxylin-eosin, Masson's trichrome stain (to detect fibrosis), Congo red stain (to detect amyloid deposits) and Prussian blue stain (to rule out cardiac hemochromatosis).

A second specimen is fixed in 2.5 percent glutaraldehyde to be processed for electron microscopy. In our center the

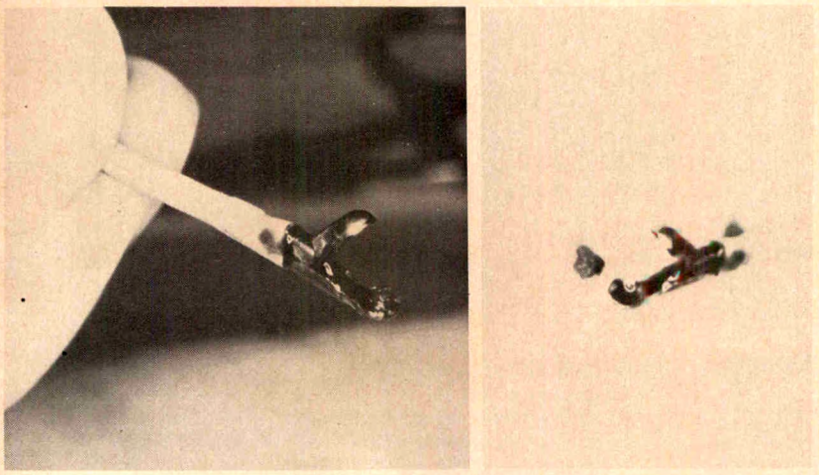


FIGURE 5. Left, the opened head of the bioptome is shown with a myocardial sample within it. **Right,** the same sample, of average size (2.5 by 3 mm), is shown on filter paper after removal from the bioptome.

tissue is scanned in thick section with light microscopy, and ultrathin sections of interesting areas are then viewed with electron microscopy and photographed for permanent record.

A third portion of myocardium is deposited in an embedding solution and rapidly frozen in isopentane and dry ice. This piece of tissue can be used for immunofluorescent staining studies and also serves as a reserve specimen should additional studies be needed. When myocarditis has been suspected, we have placed a piece of myocardium in Earle's medium for viral culture, but this has not been a rewarding practice.

Alternate Approaches for Right Ventricular Biopsy

If, for some reason, the right internal jugular vein cannot be used for biopsy, we perform right ventricular endomyocardial biopsy from one of two other sites. Left ventricular biopsy is another valid alternative.

1. Right subclavian venous approach: We have devised special equipment for cannulation of the right subclavian vein using a modification of the Seldinger percutaneous technique. For this approach the skin is punctured 0.5 cm below the inferior border of the right clavicle, lateral to the middle of the clavicle, usually at the point where the clavicle turns posteriorly and superiorly. The tissues are thoroughly infiltrated with a long needle, including the periostium of the clavicle and the first rib. We have devised a 20 gauge, 4 inch (10.16 cm) needle with a plate at the hub to improve the operator's grip (Cook, Inc.). This needle is small enough to cause little damage if the pleura or the subclavian artery is traversed. The needle is inserted into the skin at a 45° angle to a level just below the dorsal surface of the clavicle and is then brought into a horizontal plane and pointed toward the suprasternal notch. This usually results in a slightly cephalad direction of the needle, which is advanced with syringe suction until free-flowing blood is obtained from the vein. A 0.025 inch guidewire is then inserted into the vein and a specially curved sheath and dilator (Cook, Inc.) that fits snugly over the 0.025 inch (0.0635 cm) guide wire is advanced into the vein. The special curve was developed to avoid "kinking" of the sheath as it enters the right innominate vein from the subclavian vein. Manipulation of the bioptome is considerably more difficult from this approach because of the extra turn traversed by the catheter. The tricuspid valve can generally be negotiated, but it is not always possible to direct the jaws of the bioptome toward the septum. Therefore, we use this approach only when we are quite certain that the internal jugular venous approach is impossible.

2. Femoral venous approach: A long bioptome can be used from either femoral vein. However, advancing the bioptome through the great veins and across the tricuspid valve is often difficult or impossible. If such difficulty arises, a long sheath technique similar to the left heart biopsy method (see later) can be used for right ventricular biopsy. Again, accurate placement of the jaws of the bioptome against the septum is usually not possible with this method. In addition, the specimens often must be taken from a high position in the ventricle, increasing the risk of transient or permanent right bundle branch block.

Left Ventricular Endomyocardial Biopsy

Left heart biopsy using the transvenous approach was not accomplished until some time after right heart biopsy because of the large diameter of the original catheter bioptomes, anticipated problems with difficult and traumatic transarterial and transvalve manipulation of the bioptome, and the risk of clot or tissue embolization. On the other hand, the left ventricle offers the advantage of being more uniformly thick-walled than the right ventricle, making cardiac perforation less likely. In fact, we have preferred left ventricular biopsy when technical problems have rendered accurate septal positioning of the right ventricular bioptome difficult.

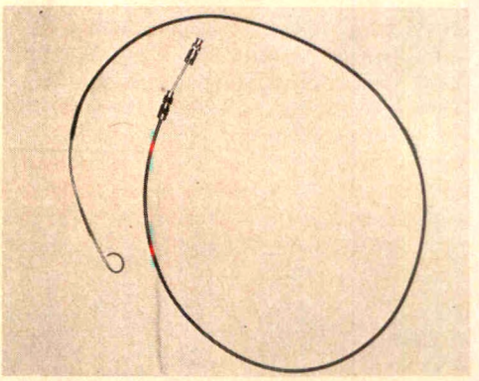


FIGURE 6. The sheath used for left ventricular biopsy is shown with a standard no. 6.7 French pigtail catheter inserted through it. This sheath is radiopaque and 90 cm in length. It has a no. 9.0 French outer diameter.

The problem of large catheter bore has been obviated by technical advances permitting biopsy with instruments of no. 7.0 French and lesser outer diameters. The St. Thomas long sheath technique has eliminated the problems associated with negotiation of arteries and aortic valve,[5] and clinical practice has demonstrated a low or probably negligible incidence rate of systemic embolization associated with left ventricular biopsy.[10]

Left femoral arterial cannulation: At our institution left ventricular biopsy is performed as described by Brooksby et al.[10] with certain modifications. The right or left femoral artery is entered with percutaneous technique, and a 0.035 inch (8.89 cm) 120 cm guide wire is introduced. A sheath and catheter are inserted over the guide wire. We use a specially prepared 90 cm radiopaque Teflon® sheath (Cook, Inc.) (Fig. 6). Other workers[10] have used a nonradiopaque sheath, but we have found that fluoroscopic visibility greatly facilitates positioning and repositioning of the sheath within the left ventricular cavity. A metal Luer Lock adaptor (Cook, Inc.) is bored out to 0.115 inch (0.2921 cm) for this sheath in order to accommodate the catheter and bioptome. A 100 cm no. 6.7 French pigtail catheter is inserted into the sheath, and the sheath-catheter combination is introduced over the guide wire and manipulated into the left ventricle. We have found the ensheathed catheter to be nearly as easily manipulated as an unemcumbered pigtail catheter.

Left ventricular bioptomes: When the left ventricle has been cannulated, the sheath is advanced over the catheter into the ventricle, and the catheter is removed. The sheath is connected to a continuous drip infusion pump when not in use. Before introduction of the bioptome, we detach the sheath from the infusion pump and allow a brisk backflow of blood to clear the sheath and to assure that the tip is not trapped against the ventricular wall. We use two left ventricular bioptomes. One is the King's endomyocardial bioptome (Key Med Ltd., Essex, United Kingdom), which is 105 cm in length and is a modification of the Olympus bronchoscopic biopsy forceps. The other is a special modification of the Stanford right ventricular bioptome, which has been lengthened to 100

cm and reduced to a 6.0 French diameter. The bioptome is advanced through the sheath and directed toward the ventricular apex. As with right ventricular biopsy, the catheter is pulled back after contact with the ventricular wall, opened, readvanced and briskly closed. Left ventricular contraction usually cannot be sensed by the operator, but ventricular contact is easily identified by inability to advance the bioptome, mild flexing of the bioptome on its attempted advancement, and the occurrence of premature ventricular contractions. Specimens obtained with left ventricular biopsy are handled exactly as described for right ventricular biopsy.

Indications: We have encountered no complications with left ventricular biopsy and have had 100 percent success in obtaining adequate tissue with this technique. We believe that the procedure is indicated when right ventricular biopsy is unsuccessful or difficult, and in certain disease states that clearly involve only the left ventricle.

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Retrograde Left Ventricular Catheterization in Patients With an Aortic Valve Prosthesis

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Twenty-seven consecutive patients with an aortic valve prosthesis were evaluated with retrograde left ventricular catheterization. The prosthesis was successfully crossed, permitting hemodynamic and angiographic evaluation of function of the prosthetic valve, left ventricle and mitral valve in all 27 cases. No complications were encountered. In patients with active endocarditis or recent embolization, the retrograde technique was avoided when possible, and attempts were made to utilize other techniques for study. However, three such patients were evaluated with the retrograde technique without complication. Examination of pressure tracings and cineangiographic films suggested only minor interference with valve poppet movement induced by the catheter traversing the valve. In three cases, hemodynamic data were recorded with the catheter crossing the prosthesis at one time and a paraprosthetic valve defect at another time. Identical gradients were recorded.

This series documents the safety and efficacy of the retrograde approach, which is proposed as an alternative to the transseptal technique and left ventricular puncture.

As survival and short-term prognosis in patients undergoing aortic valve replacement improves, an increasing number of patients are presenting with late prosthetic valve dysfunction. Several studies[1,2] have pointed to the need for precise hemodynamic and angiographic evaluation of patients with this type of valve dysfunction. The transseptal technique and direct left ventricular puncture have been considered[3] the two preferred approaches to left ventricular catheterization in patients with a prosthetic aortic valve. Unforunately many laboratories are not able to perform transseptal catheterization, and both procedures are attended by definite risks, particularly in postoperative patients. In addition, the potential complications of direct left ventricular puncture are magnified if cineangiography is needed to assess left ventricular function and mitral valve competence. Although several investigators[4,5] have demonstrated that passage of a catheter through a Starr-Edwards prosthesis placed in the tricuspid position does not significantly interfere with valve function and can be done safely, most workers have remained reluctant to attempt crossing a prosthesis on the left side of the heart. This report describes our experience with the retrograde brachial arterial approach to left ventricular catheterization in patients with an aortic valve prosthesis.

Methods

Patients: From 1972 to 1977, cardiac catheterization studies utilizing the retrograde brachial arterial technique were performed at our center in 27 patients with a prosthetic aortic valve. The indications for catheterization included congestive heart failure, major aortic regurgitation, significant hemolysis, angina pectoris and systemic embolization. Efforts were made to avoid the retrograde approach in patients with active endocarditis or recent systemic embolization, and in such patients the retrograde study was not undertaken unless other approaches failed.

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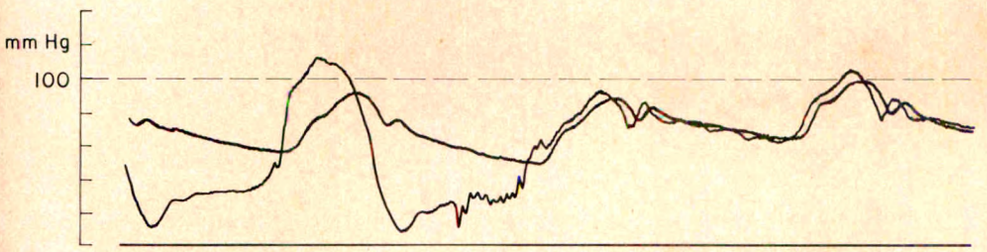


FIGURE 1. Simultaneous pressure tracings recorded during pullback of the catheter from the left ventricle to the aorta across a Starr-Edwards prosthesis. Aortic systolic pressure increased by 10 mm Hg as the catheter was removed from the prosthesis (third cycle), suggesting catheter interference with valve function (first cycle). In this patient the gradient and valve area were recalculated using the aortic pressure wave of the third cycle to account for this artifact. The change in valve area was not clinically significant.

Catheterization technique: Patients received diazepam, 10 mg orally, as premedication and were taken to the catheterization laboratory in the postabsorptive state. Arterial catheters were introduced by a right brachial arteriotomy. Systemic heparinization was used in all patients.

Starr-Edwards and Bjork-Shiley prostheses were crossed with catheters tapering to a no. 5 French tip (8F Sones, 8F Shirey) or 5F Cook and 5F Elecath polyethylene catheters. These catheters were advanced to the aortic root near the base of the prosthesis and then gently manipulated until they crossed the valve. Careful attention was paid to the motion of the poppet to ensure that there was no interference with its excursion. The left anterior oblique projection appeared to allow the best visualization for this maneuver. In several instances the smaller catheters could not be controlled well. In these cases a Teflon®-coated guide wire with a flexible tip was passed down to the end of the catheter without passing beyond the tip. The additional stiffness thus introduced was particularly useful with the no. 5F Cook and no. 5F Elecath polyethylene catheters. When the left ventricle was entered, cineangiographic films were taken in multiple projections to examine the motion of the prosthesis and poppet and to document whether the catheter had passed through the prosthesis or through a paraprosthetic leak.

Early in the course of the study we thought that the larger no. 8F angiographic catheters (Shirey and Sones) might interfere with the motion of the poppet and create an artifactually high pressure gradient. Therefore hemodynamic measurements were made with no. 5F catheters, which were then replaced with a no. 8F Shirey catheter for left ventricular angiography. However, it soon became apparent that the Shirey catheters could successfully traverse the prosthesis without significant interference with valve function. For the remainder of the study only one catheter was used for both left ventricular hemodynamic and angiographic studies. Stented heterograft valves (Hancock) were crossed with a no. 7F pigtail catheter placed over a Teflon-coated, flexible tip guide wire that was maneuvered across the valve. Once the guide wire entered the left ventricle, the catheter was advanced over it and the guide removed. The guide wire was then reinserted to remove the pigtail catheter from the left ventricle after left ventricular angiography.

Measurements: In eight patients the pressure gradient across the prosthesis was assessed with a pullback procedure. In the remaining 19 patients simultaneous aortic and left ventricular pressure measurements were recorded using a second arterial catheter placed percutaneously in the femoral artery and advanced to the aortic arch. Pressure measure-

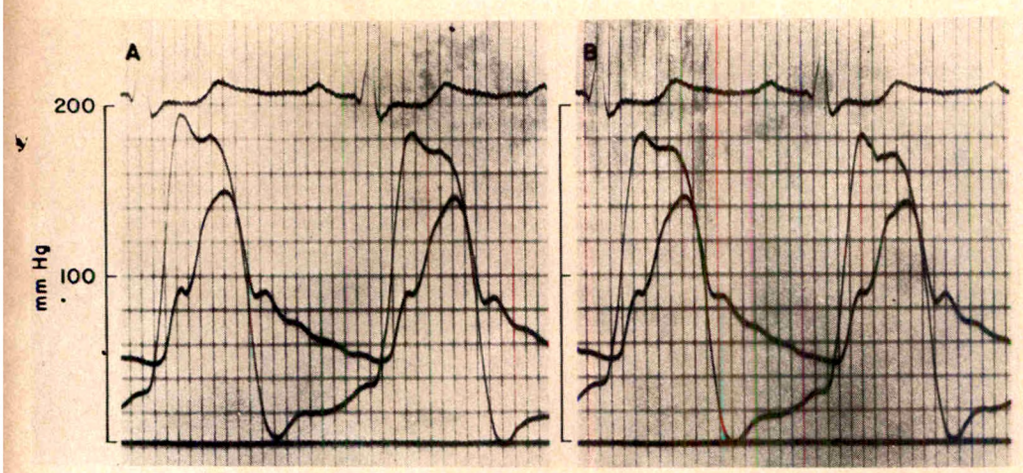


FIGURE 2. Simultaneous left ventricular and aortic pressure tracings in a patient with a Starr-Edwards aortic valve prosthesis. **Tracing A** was obtained with a no. 5F Elecath polyethylene catheter through the prosthesis and a no. 6F Cook catheter in the aortic arch. **Tracing B** was obtained 1 minute later with the same catheter through a paravalve leak. The catheter positions from which these tracings were obtained are shown in Figure 3. The pressure gradient is identical with each approach, indicating that the catheter did not impede valve function when placed through the prosthesis. In addition no difference is seen in aortic diastolic pressure, suggesting that hemodynamically significant aortic regurgitation is not produced when the catheter is in the valve ring.

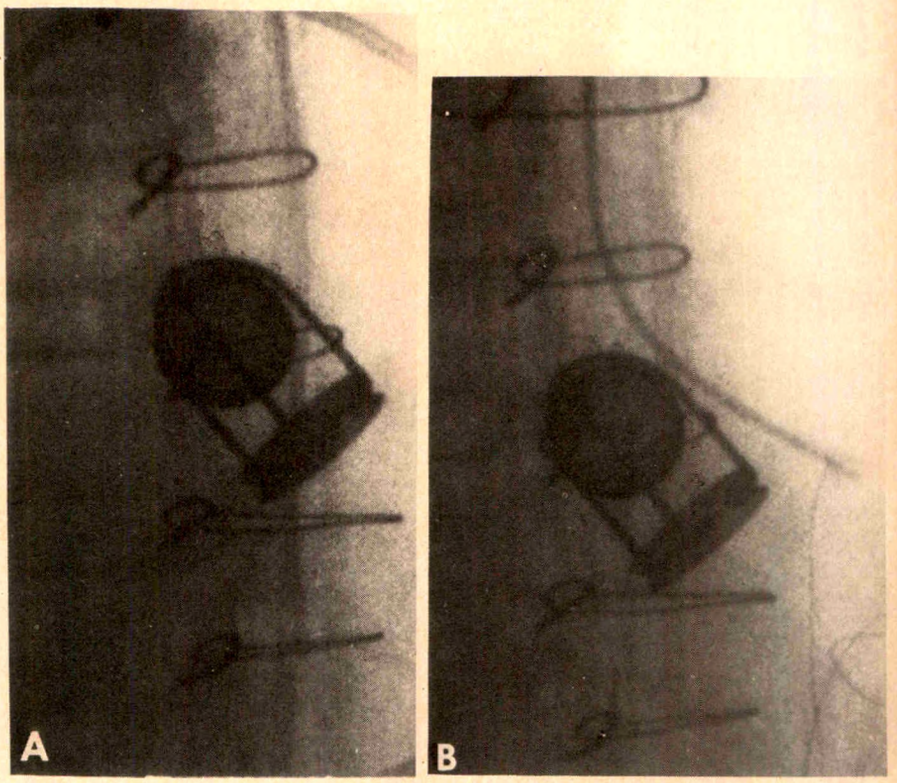


FIGURE 3. Cineangiographic films of same patient. **A,** Starr-Edwards prosthesis with a no. 5F Elecath polyethelene catheter through the valve in systole. The placement of the catheter across the prosthesis was documented with fluoroscopy in multiple views. **B,** the same prosthesis in systole with the catheter in a paravalve leak recording a ventricular pressure. Contrast injection (5 cc) documented the ventricular positioning. The systolic excursion of the poppet is normal and apparently unimpeded by the presence of the catheter.

ments were made using a fluid-filled system connected to Statham P23Db strain gauges and recorded on an Electronics for Medicine DR8 recorder. Cardiac output was determined with the Fick method, using the Scholander apparatus for expired air analysis and the Lexington Instruments LexO_2Con for blood oxygen content.[6,7] Hemodynamic determinations, left ventriculography, aortography and coronary angiography were performed in that order in all patients.

Results

Aortic valve gradients induced by the catheter: The aortic valve prosthesis was crossed in all 27 patients. The average time required for catheter manipulation was 8 minutes (range 1 to 24). Systolic pressure gradients across the prosthesis were noted in 21 of the 27 cases. The critical question with the retrograde technique is whether placement of the catheter across the prosthesis interferes with valve function and adds to any pressure gradient recorded across the valve. The degree to which the catheter itself may have interfered with function of the prosthesis and contributed to the gradient was assessed by examining the aortic pressure tracing as the catheter was passed across the valve into the left ventricle and then as it was subsequently withdrawn. In 20 of 27 patients (74 percent) no change in the systolic aortic pressure or in the configuration of the pulse wave was noted as the catheter was withdrawn from the left ventricle, suggesting that the catheter did not significantly interfere with valve function or the measured gradient. In the remaining seven patients (26 percent), the aortic pressure increased as the catheter was withdrawn, the increase averaging 12 mm Hg (range 10 to 15) (Fig. 1). This finding suggests that there was a systolic pressure gradient induced by the catheter in addition to any gradient caused by the prosthesis itself. In all seven cases, the gradient and valve area calculations were adjusted to correct for this artifact. In only one patient did this adjustment result in a clinically significant change in calculated valve area.

In three patients it was possible to cross both the prosthesis and a paraprosthetic leak (Fig. 2). In all three instances the gradient measured was the same whether the catheter was across the prosthesis or the leak, thus indicating that the catheter produced no interference with hemodynamics when it was across the prosthetic valve.

Aortic regurgitation induced by the catheter: In three patients, aortic diastolic pressure increased as the catheter was withdrawn from the prosthesis, suggesting that some aortic regurgitation had been induced by the catheter. No change in diastolic pressure was noted in the remaining cases.

In the patients with a Starr-Edwards prosthesis the cineangiographic films were examined with the catheter across the prosthesis to detect possible catheter interference with motion of the ball. In all cases the ball motion appeared to be unimpeded, with full excursion within the cage during systole (Fig. 3). However, the ball did not seat completely in diastole with the catheter across the valve. As noted, hemodynamically detectable aortic regurgitation, as estimated from pressure changes on catheter pullback, was observed in only three patients.

Aortic regurgitation with congestive heart failure or hemolysis was the most frequent manifestation of valve dysfunction, occurring in 23 cases. Critical valve stenosis was documented in only four instances.

Left ventriculography: In the patients with congestive heart failure, this state could not be assumed to have developed solely as a result of the valve defect, and left ventriculography for assessment of ventricular dysfunction or mitral incompetence was particularly crucial in these cases. Ventriculograms adequate for such evaluation were obtained in all 27 subjects. Impaired ventricular wall motion was documented in 17 cases. In 11 of these the ventricular dysfunction was present preoperatively or was associated with major aortic regurgitation through a paraprosthetic leak. The remaining six patients had less than 2+ aortic regurgitation, and the left ventricular dysfunction was due to other causes. Mitral regurgitation that was either new or significantly worse than before operation was found in eight patients, two of whom subsequently underwent mitral valve replacement.

There were no catheterization-related complications in any of the 27 patients studied.

Discussion

Our series documents the safety and efficacy of the retrograde arterial approach to the left ventricle in patients with an aortic prosthesis. The use of small catheters placed across the prosthetic valve produced only minimal interference with prosthetic function in a few cases, and in these cases the artifact could be estimated and accounted for by close examination of the arterial pressure when the left ventricular catheter was withdrawn to the aorta. In patients without major aortic regurgitation, the pressure gradients measured with this catheterization technique are in accord with those previously reported in studies using other catheterization approaches.[1,3,8–12] Left ventricular wall motion and mitral competence were successfully evaluated with angiography in all studies.

Clinical application of method: The role of this approach will have to be clarified. In our series, as in others,[1] the most frequently encountered type of valve dysfunction was a paraprosthetic leak with aortic regurgitation. In many patients with this condition the magnitude of the regurgitant flow may be sufficient to allow filling of the left ventricle with contrast medium on aortography, permitting assessment of left ventricular and mitral valve function in this manner. In such patients a case could be made against any entry into the left ventricle because the procedure would provide little additional information to aid in the therapeutic decision. However, the majority of these patients have a large stroke volume, a dilated aorta and a ventricle that does not permit adequate visualization. Direct left ventricular contrast injection has definite advantages under such circumstances.

Application in patients with active endocarditis or systemic embolism: One concern is the patient whose recent history includes either active endocarditis or systemic embolization. Such patients, it seems, would be at increased risk of embolization if the prosthesis were directly approached, and we attempted to avoid retrograde study in these patients. However, in three patients with endocarditis a retrograde study was accomplished without incident when aortography failed to visualize the ventricle adequately or when an attempt at the transseptal technique failed.

Thus, retrograde left ventricular catheterization can be accomplished effectively and safely in patients with a prosthetic aortic valve. This is of particular importance in laboratories that are unable to perform transseptal catheterization or are not willing to accept the risks of direct left ventricular puncture.

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Assessment of Cardiac Performance With Quantitative Radionuclide Angiocardiography: Right Ventricular Ejection Fraction With Reference to Findings in Chronic Obstructive Pulmonary Disease

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A reproducible noninvasive technique for measuring right ventricular ejection fraction was developed using first pass quantitative radionuclide angiocardiography. Studies were obtained in the anterior position with a computerized multicrystal scintillation camera with high count rate capabilities. Right ventricular ejection fraction was calculated on a beat to beat basis from the high frequency components of the background-corrected right ventricular time-activity curve. In 50 normal adults, right ventricular ejection fraction averaged 55 percent (range of 45 to 65 percent). This radionuclide measure of right ventricular function was reproducible, with minimal inter- and intraobserver variability, and was sensitive to changes in inotropic state induced with isoproterenol. In 36 patients with chronic obstructive pulmonary disease, right ventricular ejection fraction ranged from 19 to 71 percent. All 10 patients with cor pulmonale, as well as 9 additional patients, had an abnormal right ventricular ejection fraction. Arterial oxygen tension and forced expiratory volume were depressed significantly more in patients with abnormal right ventricular ejection fraction than in subjects with normal right ventricular function. There was no relation between abnormalities in right and left ventricular ejection fraction.

Quantitative first pass radionuclide angiocardiography has become a useful technique for noninvasive assessment of left ventricular performance in man. Methods developed in this laboratory[1] and in others[2–5] provide relatively simple means for evaluating ejection fraction, ejection rate and regional wall motion from the high frequency components of time-activity curves derived from a left ventricular region of interest. To date, with the exception of one study,[6] little attention has been given to assessment of right ventricular performance with radionuclides. The first pass radionuclide approach seems ideally suited for evaluation of right ventricular function because (1) there is temporal and anatomic separation of radioactivity within right and left heart structures, and (2) data are derived from time-activity curves rather than from outlines of cavitary silhouettes of the geometrically complex right ventricle. With this approach, both right and left ventricular performance can be evaluated concomitantly from the same examination.

This study was undertaken to develop and standardize a reproducible radionuclide angiocardiographic technique for serial assessment of right ventricular ejection fraction. To obtain high statistical reliability, a computerized multicrystal scintillation camera with high count rate capabilities was used. After the technique was developed, it was applied to the study of patients with congestive cardiomyopathy, as well as to those with chronic obstructive pulmonary disease, a clinical group in whom variable degrees of secondary right ventricular dysfunction might be anticipated.

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TABLE I

Clinical Characteristics, Pulmonary Function Data and Radionuclide Ventricular Performance Data on 36 Patients With Chronic Obstructive Pulmonary Disease

Case no.	Age (yr) & Sex	Clinical Characteristics							Medications				Arterial Blood Gases*			Pulmonary Function Tests				Nuclide Data	
		Bronch	Emph	CP	ASHD	PMD	RVF	RF	Dig	Diuretic Drugs	Bronchodil	O_2	pH	PO_2	PCO_2	FEV_1 (liters)	FVC (liters)	FEV_1/FVC	FEV_1 (% Pred.)	RVEF (%)	LVEF* (%)
1	71M	+	...	†	+	...	†	†	...	...	...	...	7.43	63	39	0.70	1.50	47	26	37	58
2	71F	+	...	+	...	...	+	+	...	+	...	+	7.46	46	34	0.95	1.38	69	67	42	24
3	77M	+	+	...	...	...	...	...	...	+	...	+	7.43	51	36	0.84	1.27	67	42	43	61
4	74M	+	+	+	...	...	+	+	+	+	+	+	7.43	34	54	0.75	2.65	28	30	36	60
5	63M	+	...	...	...	...	...	...	...	...	...	...	7.43	65	30	1.95	3.80	51	70	50	50
6	64F	+	+	...	...	...	...	...	...	...	+	...	7.43	74	38	0.50	1.40	36	26	62	83
7	58M	+	+	...	...	...	...	...	...	...	...	...	7.39	84	29	1.95	3.85	51	73	55	78
8	66F	+	+	...	...	...	...	...	+	...	+	...	7.51	45	38	1.09	1.90	57	58	53	72
9	58M	+	...	...	...	...	...	...	...	...	...	...	7.47	55	29	1.88	3.75	50	59	52	79
10	65F	+	...	...	...	...	...	...	...	...	...	...	7.47	64	36	1.10	1.65	67	60	53	60
11	69M	+	+	†	...	...	†	†	...	...	...	...	7.41	63	33	0.93	2.82	33	33	42	24
12	86M	+	...	...	...	...	...	...	...	...	...	...	7.42	65	48	1.33	2.17	61	72	64	61
13	66M	+	...	+	...	...	+	+	+	...	+	...	7.41	55	40	0.67	1.86	36	23	37	36
14	72M	+	...	...	...	...	...	...	...	...	...	...	7.43	74	38	1.21	2.60	47	69	60	59
15	84M	+	...	...	...	...	...	...	+	...	...	+	7.42	78	31	1.05	1.85	57	49	71	58
16	57M	+	...	+	...	...	+	+	+	+	...	+	7.37	49	51	0.88	1.83	48	29	37	70
17	72M	+	...	+	...	...	+	+	...	...	+	+	7.44	46	45	0.29	0.70	42	11	33	69
18	57F	+	+	...	...	...	...	...	...	+	...	...	7.48	62	33	1.84	2.67	69	79	44	61
19	52M	+	+	...	...	+	...	...	...	...	...	...	7.43	71	45	1.05	3.60	29	32	46	20
20	69M	+	+	...	...	...	...	...	+	+	+	+	7.41	57	49	0.62	1.40	44	27	65	67
21	71M	+	...	†	...	...	†	†	+	+	+	+	...	...	...	0.49	0.62	80	42	40	...
22	66M	+	+	+	+	...	+	+	+	+	+	...	7.40	56	52	0.60	2.25	27	22	30	58
23	71M	+	...	...	...	...	...	...	...	...	+	+	7.50	74	33	0.65	1.29	51	27	59	71
24	67M	+	...	+	...	...	+	+	+	...	+	...	7.47	55	35	0.65	1.29	50	35	19	62
25	61M	+	...	...	...	...	...	...	...	...	+	+	7.33	55	31	2.78	4.25	65	100	56	61
26	61M	+	+	†	+	...	†	†	...	...	...	...	7.47	64	64	1.09	2.00	26	39	44	47
27	70M	+	...	...	...	...	...	...	...	...	+	...	7.49	61	32	1.48	2.40	62	76	48	71
28	62M	+	+	+	...	...	+	+	+	+	...	...	7.51	61	30	1.70	3.55	50	59	36	76
29	56M	+	+	...	...	...	...	...	...	...	+	+	7.44	54	39	0.93	1.46	64	31	42	57
30	72M	+	...	...	...	...	...	...	+	...	+	+	7.48	52	32	1.09	2.44	54	49	48	58
31	71M	+	...	...	...	...	...	...	+	+	...	...	7.45	66	30	1.06	1.99	53	45	42	62
32	84M	+	...	...	+	...	...	...	...	...	+	+	7.42	48	47	0.82	2.35	35	43	60	29
33	79F	+	...	+	+	...	+	+	+	+	+	+	7.43	46	46	0.48	0.63	77	33	40	57
34	78M	+	...	+	...	...	...	+	+	+	+	+	7.38	45	60	0.57	1.60	36	28	34	52
35	43M	+	+	...	...	+	...	...	...	...	...	...	7.40	58	46	0.99	2.39	41	34	40	50
36	54M	+	...	...	+	...	...	...	...	...	...	...	7.48	33	56	1.63	2.30	71	54	62	65

* Arterial blood gases and left ventricular ejection fraction were unavailable in one patient (Case 21) for technical reasons.

† Development of acute cor pulmonale within 1 year of original study.

ASHD = atherosclerotic heart disease; Bronch = bronchitis; Bronchodil = oral bronchodilator; CP = cor pulmonale; Dig = digitalis preparation; Emph = emphysema; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; LVEF = left ventricular ejection fraction; O_2 = low flow oxygen therapy; PCO_2 = arterial carbon dioxide tension; PO_2 = arterial oxygen tension; PMD = primary myocardial disease; Pred. = predicted; RF = respiratory failure; RVEF = right ventricular ejection fraction; RVF = right ventricular failure.

+ = condition present.

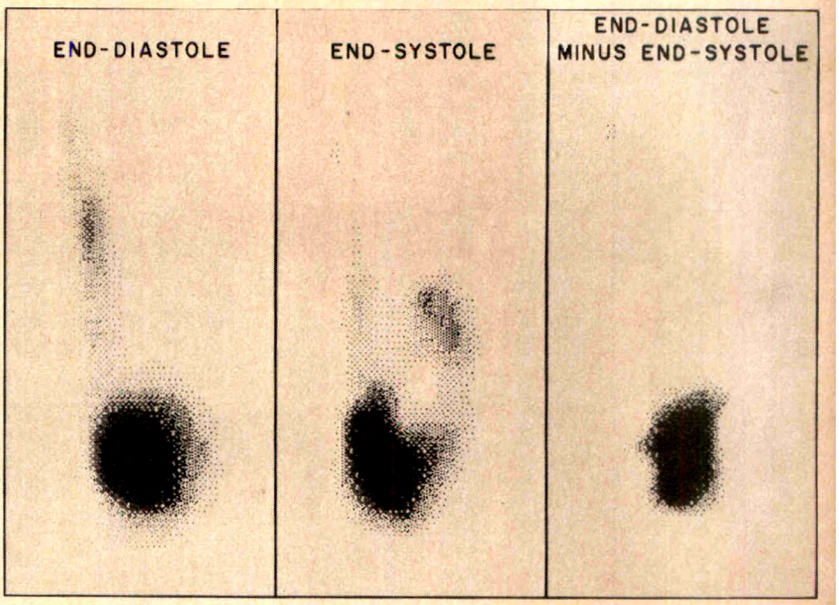


FIGURE 1. Analog computer-smoothed display of peak end-diastolic and end-systolic frames chosen from the preliminary right ventricular time-activity curve. Single frames are computer-smoothed by expansion of the original 294 matrix points in an image to 4,704 points using a linear extrapolation algorithm. The end-systolic image was subtracted from the end-diastolic image to obtain the difference image on the **right**. This frame is used to define the final right ventricular region of interest.

Methods

Patient selection: Ninety-two patients underwent a total of 103 quantitative radionuclide angiocardiograms. All patients had normal sinus rhythm at the time of study and were categorized into three clinical groups: (1) normal controls (50 subjects), (2) cardiomyopathy (six patients), and (3) chronic obstructive pulmonary disease (36 patients). Informed consent was obtained from each patient.

The 50 normal adult subjects without clinical or hemodynamic evidence of cardiopulmonary disease were evaluated to establish the normal range for radionuclide right ventricular ejection fraction. All subjects had normal electrocardiograms, upright chest radiographs and physical examinations; none were receiving cardiopulmonary medications at the time of study. Forty-four subjects were male and six female. Their mean age was 52 years (range 27 to 66). Seven normal subjects remained at rest under the scintillation camera for 20 minutes and a second radionuclide study was obtained. Comparison of these two studies allowed assessment of the reproducibility of the right ventricular function measurement. In four additional subjects, repeat radionuclide angiocardiograms were obtained during isoproterenol infusion, 20 minutes after the control study. Isoproterenol was administered intravenously (1 to 4 μg/min) until a heart rate response at least 50 percent or more above control level was achieved. Comparison of these studies allowed evaluation of the responsiveness of the radionuclide measurement to inotropic stimulation.

The six patients with documented congestive cardiomyopathy (five ischemic and one alcoholic) and recurrent congestive heart failure were studied in a clinically stable state. All were receiving digitalis and diuretic agents at the time of study. Four were male and two female. Their mean age was 64 years (range 59 to 71).

The 36 patients with chronic obstructive pulmonary disease were ambulatory and in a clinically compensated state at the time of study. Thirty were male and six female. Their mean age was 67 years (range 43 to 86). Clinical and pulmonary function data are shown in Table I. Patients had pulmonary function tests, arterial blood gas determinations, electrocardiograms and upright chest radiographs within 24 to 48 hours of the radionuclide study. Forced expiratory volume in 1 second, forced vital capacity and the ratio of forced expiratory volume to forced vital capacity were measured using a computerized flow-volume system.[7] Forced expiratory volume also was expressed as a percent of its predicted value.[8] Arterial blood gases were measured when patients were breathing ambient room air. The diagnoses of bronchitis and emphysema were based on accepted clinical criteria.[9] The diagnosis of cor pulmonale required electrocardiographic evidence of right ventricular hypertrophy[10] and a documented history of clinical decompensation resulting in acute respiratory failure and right-sided heart failure.[11]

Radionuclide technique: All studies were performed with patients supine in the anterior position. An 18 gauge 1.5 inch (3.81 cm) polyethylene catheter (Jelco) was placed in a large basilic vein in the antecubital fossa. When a single radionuclide study was performed, 15 to 20 mCi of technetium-99m pertechnetate dissolved in less than 0.5 ml of normal saline solution was placed in a 2.2 ml polyethylene tube preceded and followed by 0.1 ml air interfaces. The remainder of the tube was filled with normal saline solution, and the tube was attached with a stopcock to a syringe containing 15 ml saline solution. This system was used to introduce the bolus dose into the venous circulation. A rapidly injected discrete bolus dose is essential for satisfactory right ventricular analysis. When two sequential studies were performed, 10 to 12 mCi of technetium-99m sulfur colloid in less than 1.0 ml of normal saline solution was used for the first injection. Within 10 to 15 minutes, technetium-99m sulfur colloid is cleared completely from the blood pool by the liver and spleen. Fifteen to 17 mCi of technetium-99m pertechnetate, prepared and injected as described, was used for the second injection.

All radionuclide studies were performed in a cardiovascular nuclear imaging laboratory located within the coronary care unit. Data were obtained for 25 seconds after injection using a commercially available computerized multicrystal scintillation camera (Baird-Atomic System-77, Bedford, Massachusetts). The detector of this instrument consists of a mosaic of 294 individual crystals with a high sensitivity, parallel hole collimator (1.5 inches [3.81 cm]). Data were acquired in frame

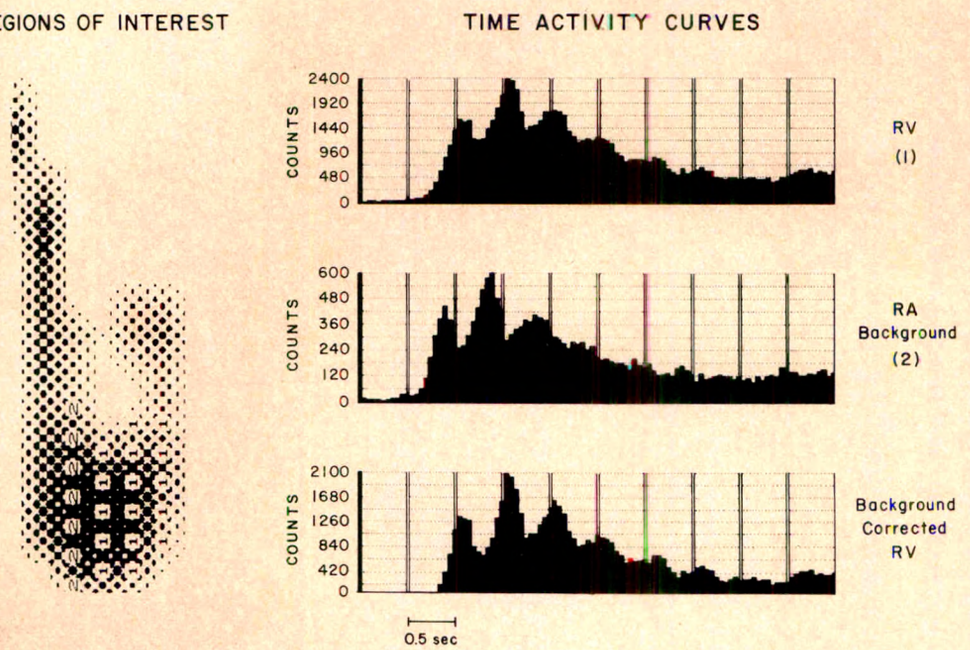


FIGURE 2. Right ventricular and right atrial background regions of interest **(left)** superimposed upon a right heart image. The numerals "1" represent the right ventricular region of interest determined as in Figure 1; the numerals "2" represent the standardized background zone. Note that peak activity in the right ventricular (RV) **(right)** curve occurs when activity in the right atrium (RA) is lowest. The background-corrected right ventricular time-activity curve was obtained by subtracting the right atrial curve from the right ventricular curve. Peak activity in the background curve is approximately one fourth of maximal right ventricular activity.

mode at 20 frames/sec with the use of a solid state buffer memory and disc.

Data processing: With the system's dedicated computer, all data were corrected for the dead time of the camera. A uniform cobalt-57 pool (New England Nuclear) was counted daily for correction of detector nonuniformity. Each study then was replayed in serial fashion and displayed on the oscilloscope with each image representing 20 summed 50 msec frames. The quality of the bolus injection was evaluated from visual assessment and time-activity curve analysis of superior vena caval inflow. Studies were utilized only when the width of this time-activity curve at 50 percent of its maximal counts was less than 1 second in duration. Only four studies were repeated because of inadequate bolus injection. The right ventricular phase was identified from the anatomic configuration and temporal appearance of the bolus dose in the central circulation.

With use of a magnetic pen and zone grid corresponding to the detector's 294 crystals, a preliminary right ventricular region of interest was selected (3 by 3 crystals at the right ventricular apex). Then a preliminary right ventricular time-activity curve was generated and used to identify the end-diastolic frame (50 msec) with the most counts and its corresponding end-systolic frame; these frames were then displayed in analog mode. In the anterior position, it is difficult to identify accurately and reproducibly the tricuspid valve plane that provides the anatomic boundary for separation of the right atrium and the right ventricle. However, by subtracting the previously chosen end-systolic image from the peak end-diastolic image, which inevitably includes portions of the right atrium, a relatively pure anatomic right ventricular region of interest can be identified (Fig. 1). This computer approach eliminates the major portion of activity originating from the right atrium and the pulmonary artery. Although some right ventricular activity may be omitted from this zone, this final region of interest, as compared with the original end-diastolic image, represents an area that corresponds solely to the right ventricle. This revised right venticular region of interest was displayed on the color television screen in a series of eight color contours, each representing a 12.5 percent gradation in count intensity. By arbitrarily zoning to the same color-coded outer margin in each patient, a reproducible right ventricular region of interest was attained.

In the anterior position, there is anatomic overlap of right ventricle and right atrium, resulting in a right atrial background contribution to the *peak* of the right ventricular time-activity curve. At this point, there is minimal, if any, pulmonary background. Therefore, a reproducible background region of interest was chosen arbitrarily as a single row of crystals (11 mm wide and the total length of right ventricle) adjacent to the right ventricle at the interface of the right atrium and right ventricle (Fig. 2). The background region of interest was not normalized to the area of the right ventricular region because such normalization would be anatomically incorrect and would be based on the assumption that the *entire* right atrium was overlapped by the right ventricle. High count rate time-activity curves were generated from the right ventricular and right atrial background zones. With the computer, the right atrial curve was subtracted temporally from the right ventricular curve, yielding a background-corrected right ventricular time-activity curve (Fig. 2).

The peak end-diastolic frame and its corresponding end-systolic frame were reidentified from this curve; if the frame numbers differed from those originally chosen, the peak and valley frames were used to generate new regions of interest and the process was reiterated. Right ventricular ejection fraction (counts at end-diastole minus counts at end-systole, divided by counts at end-diastole, times 100) was calculated on a beat to beat basis directly from the final background-corrected time-activity curve. Only beats at the peak of the time-activity curve (end-diastolic counts 70 percent of the maximal counts or greater) were used for analysis (Fig. 3). In general, one to three beats met these criteria. The final right ventricular ejection fraction represented the average of the data derived from all suitable beats.

Intraobserver variation in calculation of right ventricular ejection fraction was studied by repeating analysis of eight random studies at least 6 months after the original analysis (four patients with normal and four with abnormal right ventricular function). Interobserver variation was assessed

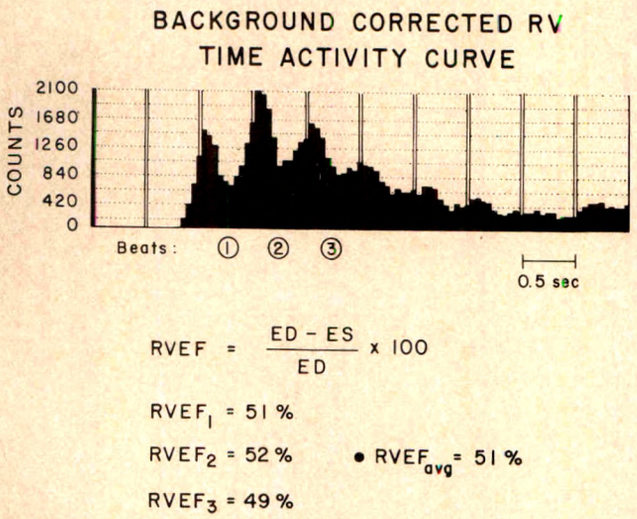


FIGURE 3. Beat to beat calculation of the right ventricular ejection fraction in the patient whose data are shown in Figures 1 and 2. Right ventricular ejection fraction (RVEF) is determined from counts at end-diastole (ED) minus counts at end-systole (ES), divided by counts at end-diastole, times 100. avg = average.

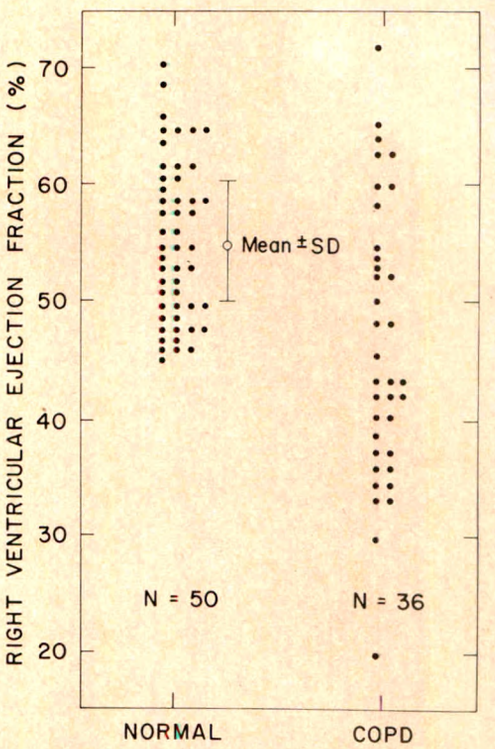


FIGURE 4. Right ventricular ejection fraction in 50 normal adult subjects without cardiopulmonary disease and 36 patients with chronic obstructive pulmonary disease (COPD). The normal range, expressed as ± 2 standard deviations (SD) from the mean, is 45 to 65 percent. In patients with chronic obstructive pulmonary disease, right ventricular ejection fraction ranged from 19 to 71 percent and was abnormal (less than 45 percent) in 19. N = number of patients.

from a comparison of the analyses of these eight studies by two independent observers.

Left ventricular performance: By redisplaying the original serial playback, the left ventricular phase can be readily identified from the anatomic configuration and temporal appearance of the bolus dose as it passes through the central circulation. The left ventricular ejection fraction was determined with previously reported techniques from the same angiocardiogram used to determine the right ventricular ejection fraction.[1]

Statistical methods: The data are represented as mean values ± standard error of the mean unless otherwise stated. Clinical and pulmonary function data were compared among patient groups using Student's t test. Reproducibility and observer variability were analyzed using a paired t test. When more than one beat was used to calculate the right ventricular ejection fraction of a patient, the standard deviation of the single beat analyses was determined. This represents the beat to beat variability for that patient. The mean of the individual standard deviations was used as an index of the overall beat to beat variability of the technique. Correlation coefficients were obtained from standard regression equations.[12]

Results

Normal range of right ventricular ejection fraction: In the 50 clinically normal adults, right ventricular ejection fraction ranged from 45 to 71percent (mean 55 percent) (Fig. 4). The normal range, defined as the mean ± 2 standard deviations, was 45 to 65 percent. Thus, the lower limit of normal by this technique is considered 45 percent. Left ventricular ejection fraction assessed from the same radionuclide study used to assess right ventricular function was normal (more than 55 percent) in all subjects (average 69 percent, range 58 to 70 percent). Right ventricular ejection fraction was less than left ventricular ejection fraction in 44 of 50 subjects and did not correlate with left ventricular ejection fraction ($r = 0.31$).

Reproducibility: In the seven normal subjects studied sequentially, initial right ventricular ejection fraction averaged 51 ± 2 percent, which was not significantly different from the value in the repeat study (52 ± 2 percent $P > 0.05$). Right ventricular ejection fraction ranged from 0 to 3 percent (mean, 2 percent) in individual subjects.

Intervention studies: Infusion of isoproterenol in four normal subjects increased heart rate from 71 ± 6 to 119 ± 5 beats/min ($P < 0.001$). Right ventricular ejection fraction increased from 49 ± 2 to 58 ± 1 percent ($P < 0.001$), and left ventricular ejection fraction increased from 70 ± 1 to 80 ± 2 percent ($P < 0.001$).

Data processing: In all patients studied, counts in the peak end-diastolic frame from the background-corrected right ventricular time-activity curve averaged 2,340 ± 520. These count rates are comparable with those obtained with the left ventricular "representative" cardiac cycle[1] and provide sufficient count densities for high statistical certainty.

At least two cardiac cycles were used for analysis of right ventricular ejection fraction in 76 of 103 radionuclide studies. Within individual patients, single beat analyses of right ventricular ejection fraction differed up to 12 percent from the mean value. In these studies, right ventricular ejection fraction calculated from the

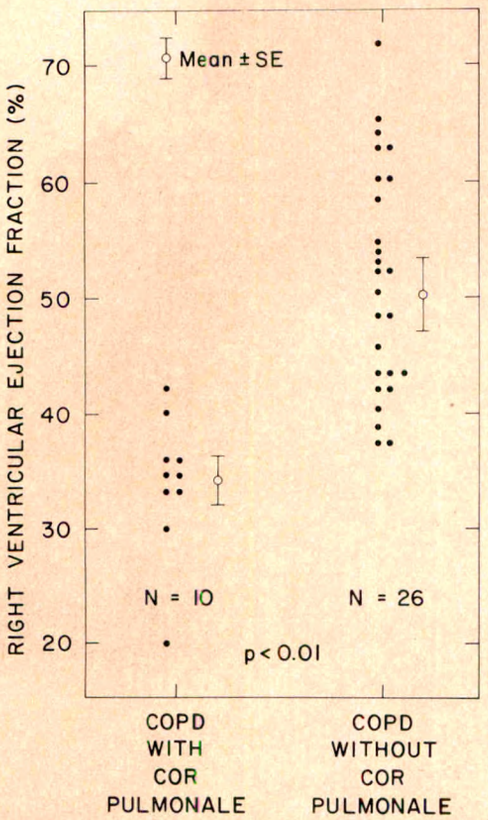


FIGURE 5. Right ventricular ejection fraction in patients with chronic obstructive pulmonary disease (COPD) with or without cor pulmonale. All patients with cor pulmonale had an abnormal right ventricular ejection fraction; however, nine additional patients without cor pulmonale also had depressed right ventricular function. N = number of patients; p = probability; SE = standard error.

first acceptable beat averaged 50 ± 6 percent and from the last beat, 47 ± 7 percent ($P > 0.05$). The pooled standard deviation for beat to beat measurement of right ventricular ejection fraction was ± 4 percent.

Repeat analysis of eight studies demonstrated minimal intra- and interobserver variability in the calculation of right ventricular ejection fraction. The difference between original and second determinations of right ventricular ejection fraction by the same observer ranged from 1 to 5 percent (mean 3 percent, $P > 0.05$). Analysis by a second observer differed by 2 to 8 percent (mean 5 percent, $P > 0.05$) in comparison with the original value.

Cardiomyopathy: Right ventricular ejection fraction was abnormal in each of the six patients with cardiomyopathy and averaged 38 ± 2 percent (range 32 to 43 percent), which was significantly less than that of the normal subjects ($P < 0.001$) or the entire group with chronic obstructive pulmonary disease ($P < 0.01$). Left ventricular ejection fraction averaged 29 ± 3 percent (range 20 to 38 percent), which also was significantly less than that of the normal subjects ($P < 0.001$).

Chronic obstructive pulmonary disease: Right ventricular ejection fraction varied widely in the 36 patients with chronic obstructive pulmonary disease, ranging from 19 to 71 percent (Fig. 4). This index of right ventricular function was abnormal in 19 patients (38 ± 2 percent) and normal in 17 patients (57 ± 2 percent). In the 10 patients with cor pulmonale, right ventricular ejection fraction averaged 35 ± 2 percent (range 19 to 42 percent) which is significantly lower than that of the remaining patients ($P < 0.05$). All patients with cor pulmonale had a depressed right ventricular ejection fraction (Fig. 5). However, 9 of 26 patients without clinical evidence of cor pulmonale, but with severe ventilatory impairment, also had a depressed right ventricular ejection fraction. Of these nine patients, four (Cases 1, 11, 21 and 26) subsequently had acute respiratory decompensation and cor pulmonale, whereas no patient with a normal right ventricular ejection fraction had cor pulmonale within 1 year of the original study (Table I).

Forced expiratory volume averaged 1.1 ± 0.1 liters in the entire group of 36 patients with chronic obstructive pulmonary disease. Arterial oxygen and carbon dioxide tensions averaged 58 ± 2 and 40 ± 2 mm Hg, respectively. If the 36 patients are separated into those with severe pulmonary impairment (forced expiratory volume less than 1 liter) and those with only moderate impairment (forced expiratory volume 1 liter or more), a striking relation between pulmonary function and right ventricular performance becomes evident. Fourteen of 19 patients with a forced expiratory volume of less than 1 liter had a depressed right ventricular ejection fraction. In these 19 patients, right ventricular ejection fraction averaged 42 ± 3 percent, which is significantly less than that in the 17 patients with forced expiratory volume of 1 liter or more (52 ± 2 percent, $P < 0.01$).

When approached in an alternative way, forced expiratory volume was 37 ± 4 percent of predicted value in patients with an abnormal right ventricular ejection fraction and 54 ± 4 percent of predicted value in the remaining patients ($P < 0.001$) (Fig. 6). Similar significant differences were evident for forced vital capacity and arterial oxygen tension, but not for pH or arterial carbon dioxide tension. However, pulmonary function data did not completely separate patients with normal and abnormal right ventricular ejection fraction.

Relation of left and right ventricular performance: In contrast to the pulmonary function data, left ventricular ejection fraction did not differ significantly in patients with either abnormal or normal right ventricular function (Fig. 6). Furthermore, there was no meaningful correlation between right and left ventricular ejection fraction in patients with chronic obstructive pulmonary disease ($r = 0.18$). Left ventricular ejection fraction ranged from 20 to 78 percent (mean 58 percent) and was abnormal in only nine patients. Atherosclerotic cardiovascular disease or primary myocardial disease was present in six of these nine patients and could explain their left ventricular dysfunction. In the remaining three (Cases 2, 5, 11), the cause of the left ventricular dysfunction was not apparent clinically. In the 10 patients with cor pulmonale and severe right ventricular dysfunction, left ventricular ejection frac-

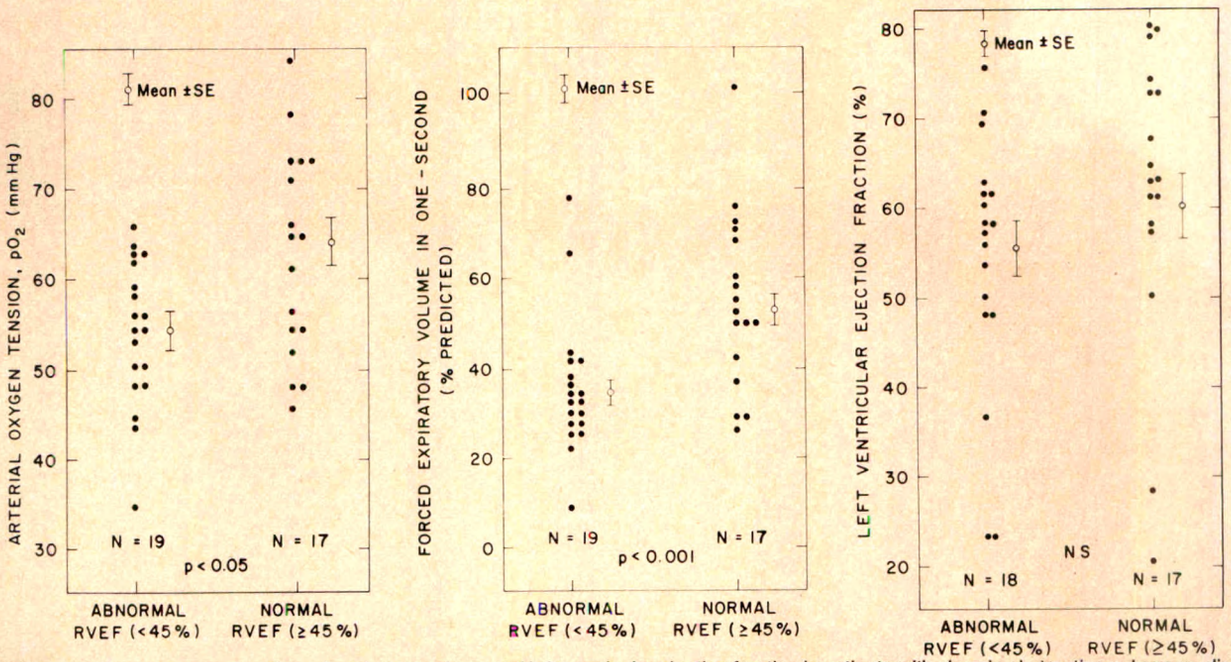


FIGURE 6. Arterial oxygen tension, forced expiratory volume and left ventricular ejection fraction in patients with chronic obstructive pulmonary disease. Patients are grouped according to right ventricular ejection fraction (RVEF). Forced expiratory volume (percent predicted) and arterial oxygen tension were significantly lower in patients with an abnormal right ventricular ejection fraction than in those with normal right ventricular function. In contrast, there was no direct relation between the presence of abnormal right and left ventricular ejection fraction. N = number of patients; p = probability; SE = standard error.

tion averaged 56 ± 5 percent (range 24 to 76 percent) and was normal in 6 of 10.

Discussion

This noninvasive study has demonstrated the feasibility of determining right ventricular ejection fraction from temporally and anatomically separated portions of the same first pass angiocardiogram used to assess left ventricular function. The measurement of right ventricular ejection fraction appears to be reproducible and can be obtained with minimal inter- and intraobserver variability when patients have normal sinus rhythm. The technique developed for assessing right ventricular ejection fraction is similar to that used to determine left ventricular function; both employ high frequency regional time-activity curves derived through iterative processes.[1] In these radionuclide studies, changes in radioactive count rates correspond to changes in chamber volume. The major assumption of this first pass technique is homogeneous mixing of the radioactive tracer with blood.[13] On the basis of previous indicator-dilution studies, adequate mixing should be expected after peripheral venous injection.[13,14]

Contrast angiography has been applied to the calculation of right ventricular volumes; however, there has been wide variation in published normal values and lack of agreement on the optimal technique.[15] Correlative contrast angiographic data were not obtained as part of the validation of the radionuclide technique presented in our report. However, right ventricular ejection fraction determined from first pass radionuclide studies was sensitive to inotropic stimulation and correlated well with other pathophysiologic indexes of chronic obstructive pulmonary disease.

Problems in determination of right ventricular volumes: The difficulties encountered in contrast angiographic assessment of right ventricular volumes are due predominantly to the irregular shape and borders of the right ventricular cavitary silhouette. The trabeculated right ventricle does not correspond to a conventional geometric form; its three dimensional shape has been approximated by prisms,[16] pyramids,[17] parallelopipeds [18] and ellipses.[18,19] Biplanar area-length calculations also have been applied to right ventricular volume analysis.[18–20] An alternative approach, which does not require assumption of a particular geometric shape, involves use of Simpson's rule for calculation of volumes.[16,20–22] Determinations based upon each of these approaches have correlated well with data derived from postmortem casts. However, it has been suggested that the irregular shape of the right ventricle, especially when dilated, may preclude accurate analysis of right ventricular volumes from two projections alone using any approach.[15] Even with these potential problems, contrast angiographic determination of right ventricular ejection fraction has been used in the study of patients with congenital[16,19–22] and coronary[17,21] heart disease and has provided useful clinical information on these patients. However, relatively few adults have been studied with any of these contrast techniques.[17,21] Gentzler et al.[21] found a mean normal right ventricular ejection fraction of 51 percent (range [mean ± 2 standard deviations] 35 to 67 percent) in eight adults, whereas Ferlinz et al.[17] found a mean of 66 percent

(range 54 to 78 percent) in nine adults. Mean data on normal children from four additional angiographic studies were between 61 and 64 percent.[16,19,20,22] In our radionuclide study, the data on a group of 50 adults without cardiopulmonary disease yielded an average normal value for right ventricular ejection fraction of 55 percent (range 45 to 65 percent). These values are similar to those obtained by Steele et al.[6] using radionuclide techniques and are not dependent upon geometric assumptions concerning the shape of the right ventricle. The absolute value obtained for right ventricular ejection fraction may not correspond precisely with in vivo ventricular volumes; however, this radionuclide index of right heart function allows categorization of patients and reproducible sequential study of right ventricular performance.

Reliability of radionuclide method: Of prime importance in establishing the reliability of the technique is the peak count rate attained. In calculating ejection fraction on a beat to beat basis, high count rates are essential for adequate statistical certainty and are especially important in assessing patients with an abnormally low ejection fraction, such as the patients in this series with cor pulmonale. The computerized multicrystal scintillation camera employed for these studies allows accumulation of up to 250,000 counts/sec in the right heart image and average peak end-diastolic counts from the right ventricular region of interest of more than 2,000 counts/data frame (50 msec). The statistical uncertainty of such count rates is less than ± 3 percent. At present, such high count rates cannot be attained with conventional gamma cameras, and thus application of this technique to other systems may be limited.

The anterior position was chosen for all studies, because it places the patient's heart closest to the detector, thereby maximizing efficiency of count detection for both the right and left heart phases. Although the right anterior oblique position offers maximal separation between the right atrium and the right ventricle, it places the left ventricle farther away from the detector, decreases count detection during the left heart phase and makes this portion of the study technically less satisfactory. Zoning of the end-diastolic frames to define the right ventricular region of interest results in a zone that must include activity outside of the right ventricle. For this reason we used the image subtraction approach to define a reproducible and relatively pure anatomic right ventricular region of interest.

The contribution of background radiation during the right heart phase is clearly less than during the left heart phase and fluctuates from beat to beat as well as during each beat itself. When the peak of the radionuclide bolus dose is in the right ventricle, the major source of background is the right atrium, with relatively few counts originating from the pulmonary vascular bed. The choice of a single row of crystals to define the right atrial background contribution was made empirically. Peak activity in the background curve averages approximately 25 percent of peak right ventricular activity. This reproducible background region of interest lies at the interface of the right atrium and right ventricle and is at the anatomic location where the major background contribution intuitively would be expected to arise.

Right and left ejection fractions in chronic obstructive pulmonary disease: In our study, right and left ventricular ejection fraction were assessed in patients with chronic obstructive pulmonary disease. Abnormal right ventricular ejection fraction was present in all patients with clinical and electrocardiographic evidence of cor pulmonale; however, right ventricular ejection fraction varied widely in patients with chronic obstructive pulmonary disease, being normal in 17 patients and abnormal in 19 others. These findings are in agreement with preliminary data from Ellis et al.[23] using similar techniques. Right ventricular dysfunction as evidenced by abnormal right ventricular ejection fraction, but without clinical signs of right heart failure or right ventricular hypertrophy, was noted in 9 of 36 patients, 4 of whom had subsequent decompensation. This finding suggests that the technique may be sensitive for early detection of right ventricular dysfunction before the development of cor pulmonale, at a time when it would not be appreciated by conventional clinical evaluation.

A simple relation between left and right ventricular ejection fraction in chronic obstructive pulmonary disease was not evident. In all but nine patients, normal left ventricular ejection fraction was preserved, and in six of these, other cardiac causes could be evoked to explain the depression in left ventricular performance. This finding of essentially normal left ventricular ejection fraction in chronic obstructive pulmonary disease is in agreement with earlier data from studies using the bedside probe.[24,25] Other clinicopathologic studies have presented conflicting data concerning possible left ventricular dysfunction in chronic obstructive pulmonary disease.[26–28]

Implications: This noninvasive radionuclide technique provides a means for assessing right ventricular performance and has been used in the characterization of patients with chronic obstructive pulmonary disease. These studies take only a short period of time to perform and are directly applicable to the acutely ill patient. Preliminary results indicate that this approach also allows assessment of the effect of pharmacologic interventions, such as aminophylline in this patient group.[29] In addition, the technique has been shown to be equally applicable to the study of patients with ischemic heart disease, specifically inferior wall myocardial infarction,[30] and it also appears to be useful in patients with primary myocardial disease or congenital abnormalities predominantly affecting the right ventricle.

Acknowledgment

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Primary Repair of Complete Atrioventricular Canal in Patients Less Than 2 Years Old

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Twenty-seven consecutive patients less than 2 years of age underwent primary intracardiac repair of complete atrioventricular (A-V) canal. Three (19 percent) of the 16 operated on after January 1, 1975 died in the hospital, a smaller proportion than the 8 of 11 patients who died in the hospital after operation between 1972 and 1975 ($P = 0.005$). The date of operation as a continuous variable is also related to the probability of hospital death ($P = 0.016$). Age at operation was not related to hospital mortality among the total group of 27 infants, nor were the anatomic characteristics of the anterior and posterior bridging leaflets, the location and size of the interventricular communications or the duration or technique of profound hypothermia (total circulatory arrest versus low perfusion flow rate). The improved results in the 16 patients operated on since January 1, 1975 are believed to be primarily the result of an improved ability to construct "mitral" and "tricuspid" valves from the common A-V valve. Fourteen of the 16 hospital survivors are alive and well 5 to 60 months after operation. These results and the natural history of patients with this malformation indicate that there should be no change in the policy of performing elective intracardiac repair before age 2 years and primary repair rather than pulmonary arterial banding when operation is required in the early months of life.

Early primary repair of many cardiac malformations predisposing to pulmonary vascular disease is now being performed with good results.[1–3] In support of the recent data of others[4–7] concerning the good results possible from early primary repair in patients with complete atrioventricular (A-V) canal, we report the results of our policy, implemented in 1972, of performing primary repair of complete A-V canal in even very young infants, if they are seriously ill, and elective repair before age 2 years. In the early years of the application of this policy, the early mortality rate was high. Once certain modifications of concepts and techniques were made, the results became much better.

Material and Methods

Patients: Between September 1, 1967 and October 1, 1976, there were 48 patients with complete A-V canal who underwent 49 operations at this center (Table I). Thirty-six of these patients had undergone no previous operations, had no major associated cardiovascular anomalies and underwent complete primary repair. Twenty-seven of these 36 patients were less than 24 months of age at the time of operation and constitute the study group. All of this subset of 27 patients were operated on after January 1, 1972. Eight (30 percent) had mongolism, six (22 percent) had a patent ductus arteriosus and two had a persistent left superior vena cava.

All 27 patients were studied preoperatively with cardiac catheterization and angiocardiography. Preoperatively, 24 patients had congestive heart failure that was of severe degree in 9. Five of these 24 patients also had severe retardation of growth. The only symptoms in two patients were frequent upper respiratory infections and pneumonia. One patient was asymptomatic.

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Surgical procedure: Most of the operations were performed with profound hypothermia and a period of low perfusion flow rate (0.5 liters·min^{-1}·m^{-2}) or total circulatory arrest. Two venous cannulas were usually used, so that the right atriotomy could be made and exposure arranged during cooling and the atrium closed during rewarming. We did not use cold cardioplegic myocardial preservation at the time these patients were operated on. Postoperative care included nasotracheal intubation and controlled or intermittent mandatory ventilation for a median time of 1 day postoperatively and intensive treatment of the cardiovascular system when indicated by low cardiac output. Autopsy was performed in 9 of the 11 patients less than 2 years of age who died early postoperatively.

Follow-up: Information was obtained from a systematic review of the patient's postoperative visit records, correspondence with each patient's personal physician and telephone conversations with the patient's family. The date of follow-up is March 1, 1977, allowing for each patient a minimal follow-up time of 5 months. None of the 16 hospital survivors less than 2 years of age at the time of operation has been lost to follow-up study.

Statistical analysis of factors related to mortality: The relation of several variables to hospital mortality was statistically analyzed. The influence of age at operation, date of operation and preoperative hemodynamic state was analyzed using probability of event techniques.[8,9] The influence of anatomic variables, such as size of the ventricular septal defect and the anatomy of the bridging leaflets, was evaluated using Fisher's exact test for a contingency table.[10] The influence of quantitative variables, such as the duration of operative ischemic arrest, was analyzed using the unpaired t test. The age-specific probability of hospital death was recalculated[8,9] using (1) the age and hospital mortality status of each patient in the study group operated on between 1975 and October 1976, and (2) the hospital mortality (2 in 27) of patients 2 years of age and older operated on at the Mayo Clinic.[11] The median age for these patients was assumed to be 60 months. (The average age is known to be 7 years, the youngest age 3 years and the oldest 18, and the two deaths are known to have occurred in patients aged 3 and 18 years, respectively).

Quantitative variables are presented with their mean ± 1 standard deviation. Proportions are presented with their 70 percent confidence limits using the quadratic approximation given by Wallis and Roberts.[12] Age at operation and the duration of the follow-up period were calculated by conversion of all dates to Julian days and subtracting.*

* Because the Julian calendar is presented in days, we followed the usual convention of taking 365.2425 days as 1 year, and 1/12 of a year as 1 month.

TABLE I

Operations for Complete Atrioventricular (A-V) Canal in [S,D,D,] or [I,L,L] Hearts (1967 to October 1976)

Lesions	Cases (no.)	Hospital Deaths no.	Hospital Deaths %
Complete A-V canal			
Primary repair	36	13	36
Secondary repair after banding	3	2	67
PA banding	3*	1	33
Complete A-V canal + coarctation	1†	1	100
Tetralogy of Fallot with complete A-V canal	5	3‡	60
DORV with complete A-V canal	1	1§	100

* One patient is also included under Secondary repair after banding.
† Simultaneous repair of both.
‡ One patient also had multiple muscular ventricular septal defects and previously had undergone Waterston and Blalock-Taussig anastomoses.
§ The patient also had an [I,L,L] heart with bilateral superior venae cavae, total anomalous pulmonary venous connection to the left superior vena cava-atrial junction, absent coronary sinus, common atrium, and valve and subvalve pulmonary stenosis. Only palliative pulmonary valvotomy and infundibular resection were performed.
DORV = double outlet right ventricle; PA = pulmonary artery.

Results

Early Results

Mortality: Three patients (19 percent, confidence limits 8 to 34 percent)* of 16 patients less than 2 years of age operated on from January 1975 to October 1976 died in the hospital after primary repair of complete A-V canal. This mortality rate is significantly lower than that of 8 of 11 patients operated on before 1975 (P = 0.005) (Table II). The date of operation as a continuous variable is significantly related (P = 0.016) to the probability of hospital death among the total group of 27 infants operated on in the total period (Fig. 1).

The three hospital deaths among the 16 patients operated on in 1975 and 1976 occurred in infants aged

* In this paper, confidence limits refers to the 70 percent confidence limits of proportions and probability of event analyses, calculated as described under Methods. This indicates the degree of uncertainty imposed by the size of the sample, and corresponds to 1 standard error as applied to continuous variables.

TABLE II

Primary Repair of Complete Atrioventricular (A-V) Canal in Patients Less Than 2 Years Old

Age (mo)	1967 to 1975* Total no.	Hospital Deaths no.	%	CL (%)	1975 to October 1976* Total no.	Hospital Deaths no.	%	CL (%)
<3	1	1	100	13–100	2†	1	50	7–93
3 to <6	1	—	0	0–87	6†	2	33	12–62
6 to <12	2	2	100	39–100	3†	0	0	0–47
12 to <24	7‡	5	71	45–90	5	0	0	0–32
Total	11	8	73	53–88	16	3	19	8–34

* P probability (P) value for the difference between the two time periods = 0.005.
† In these 11 patients (aged less than 12 months) there were three deaths (mortality rate 27 percent; 70 percent confidence limits 12 to 47 percent).
‡ One patient had the intermediate form of A-V canal.
CL = 70 percent confidence limits.

TABLE III

Primary Repair of Complete Atrioventricular Canal at Age 2 or More Years (1967 to October 1976)

Age (yr)	Patients (no.)	Hospital Deaths		
		no.	%	CL (%)
2 to <5	1	0	0	0–87
5 to <10	6	2	33	12–62
>10	2	0	0	0–61
Total	9	2	22	8–45

CL = 70 percent confidence limits.

TABLE IV

Primary Repair of Complete Atrioventricular Canal Before Age 24 Months (1972 to October 1976)

Hemodynamic Variables	Entire Group		Hospital Survivors		Hospital Deaths	
	Mean ±SD	no.	Mean ±SD	no.	Mean ±SD	no.
PVR	5.5 ± 3.13	26	5.6 ± 3.79	15	5.3 ± 2.09	11
$P_{\overline{PA}}$	43.8 ± 9.17	27	44.0 ± 10.83	16	43.5 ± 6.53	11
Q_p/Q_s	2.7 ± 1.27	26	2.8 ± 1.58	15	2.6 ± 0.70	11

P_{PA} = mean pulmonary arterial pressure in mm Hg; PVR = pulmonary vascular resistance in units·m^2; Qp/Qs = ratio of pulmonary to systemic blood flows; SD = standard deviation.

1.2, 3.7 and 4.9 months, respectively. None of the three had elevation of mean left atrial pressure, large *V* waves in the left atrial pressure pulse or other evidence of significant mitral regurgitation in the postoperative period. The youngest of the three patients, who had severe congestive heart failure preoperatively, died with low cardiac output on the 2nd postoperative day. Autopsy revealed the repair to be intact. The 3.7 month old patient, who had a pulmonary vascular resistance of 9 units·m^2 and pulmonary sequestration of the right lower lobe, died on the first postoperative day of low cardiac output that was unresponsive to intensive therapy. No autopsy was obtained. The 4.9 month old patient, whose operation was an emergency procedure performed because of severe pulmonary edema, had a patent ductus arteriosus ligated at the time of repair of the complete A-V canal. Postoperatively, she had low cardiac output and required support with catecholamines from the early postoperative period until her death on the 7th postoperative day. On the 3rd postoperative day, she sustained a ventricular arrhythmia followed by seizures and was comatose from that time until her death. Autopsy showed the repair to be intact.

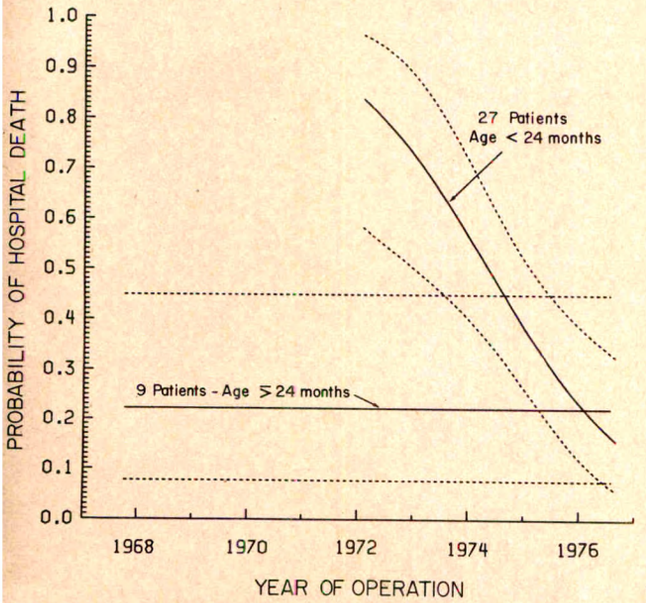


FIGURE 1. The probability of hospital death after primary repair of complete A-V canal for each year in which the operation was performed. The **solid line** is the mean value and the **dotted lines** enclose the 70 percent confidence bands. Although hospital mortality was unchanged during this period in patients over age 2 years, attention must be given to the broad confidence bands. The proportion of infants (under age 2 years) who died in the hospital was high in 1972 and 1973 but did not differ from that of older children by 1975. Logistic equation for probability (Pr) of hospital death: $Pr = 1./(1. + \exp\{-5.378 \pm 2.6166 + 0.06067 \pm 0.027323$ [date of operation (in months since January 1, 1967)]$\}$); $P_0 = 0.04$; $P_1 = 0.03$; $r_{0,1} = -0.986$.

Age and mortality: Age at operation, as a continuous variable, was not related to hospital mortality in the overall group of 27 infants ($P = 0.96$). Further, the hospital mortality rate of the 16 infants operated on in 1975 and 1976 is not significantly different ($P = 0.77$) from that of the 9 patients aged 2 years or older* operated on between 1967 and October 1976 (Table III). Hospital mortality in the older patients was not demonstrably related to the date of operation (Fig. 1).

Other factors related to mortality: Analysis was made of the relation of certain variables to hospital mortality in the total group of 27 infants (16 operated on in 1975 and 1976 and 11 between 1972 and 1975). No relation was found between hospital mortality and preoperative mean pulmonary arterial pressure ($P = 0.88$) or pulmonary vascular resistance ($P = 0.79$) (Table IV). The anatomic characteristics of the anterior and posterior bridging leaflets were also unrelated to hospital mortality among these infants and did not significantly differ from the characteristics found in the 11 older patients operated on between 1967 and October 1976 (Table V). The surgeon's operative note indicated the presence of "deficient" A-V leaflet tissue or a small mitral orifice after repair in 7 of the 11 patients (64 percent) operated on before January 1975 and in only 3 of the 16 patients (19 percent) operated on after that date ($P = 0.02$). The location and size of the interventricular communications (Table VI) were not related to hospital mortality in the infant group ($P = 0.39$ and P

* One 69 month old boy, operated on in 1967, died 12 hours postoperatively with hyperthermia, hypotension and finally ventricular tachycardia. An 83 month old child with mongolism whose mean pulonary arterial pressure after repair was the same as aortic died on the 3rd postoperative day. Autopsy showed severe pulmonary vascular disease.

TABLE V

Primary Repair of Complete Atrioventricular Canal (1972 to October 1976)

Bridging Leaflet	Age <24 Months no.	%	Age ≥24 Months no.	%	Significance*
Anterior					0.9
Free-floating	5	19	3	33	
Tethered	21	81	6	67	
Posterior					0.8
Free-floating†	2‡	8	1	11	
Tethered	24	92	8	89	

* Of anatomic distribution with respect to age (probability [*P*] value).
† We recognize the rarity of this type of posterior bridging leaflet, but it was so described in the operative note.
‡ Does not include the single patient with the intermediate form of atrioventricular canal.

TABLE VI

Primary Repair of Complete Atrioventricular Canal (1972 to October 1976): Location and Size of Interventricular Communications

Extension of VSD Beneath Bridging Leaflet	Age <24 Months* no.	%	Age ≥24 Months† no.	%
Anterior				
None	1‡	4		
Small	1	4	1	12
Medium	8	31	5	62
Large	16	62	2	25
			$P = 0.08$	
Posterior				
None	5	19		
Fenestration	. . .	. . .	1	12
Small	3	12	1	12
Medium	5	19	3	38
Large	13	50	3	38

* Data available in 26 of 27 patients.
† Data available in eight of nine patients.
‡ Patient had the intermediate form of atrioventricular canal.
VSD = ventricular septal defect.

= 0.34 for communications under the anterior and posterior bridging leaflets, respectively). Most of the infants had a large defect beneath at least one of the bridging leaflets. The incidence of large defects beneath the anterior bridging leaflet was significantly greater in the infants than in the older patients.

Profound hypothermia with a single period of circulatory arrest or low flow perfusion (0.5 liters·min^{-1}·m^{-2}) was used in 24 of the 27 infants (Table VII). Hospital mortality among these infants was not related to the duration of low flow ($P = 0.5$) or of total circulatory arrest ($P = 0.3$). Survival was not demonstrably related to the use of total circulatory arrest as opposed to low flow ($P = 0.13$). The two techniques were not used in a differing proportion of infants during the two time periods ($P = 0.41$).

No instances of permanent complete heart block postoperatively were seen among the 27 infants. No patient had a prosthetic valve inserted.

Late Results

Late deaths: Two infants died late postoperatively. One 6 month old boy with mongolism had severe congestive heart failure preoperatively and some difficulty with pulmonary dysfunction in the early postoperative period. At discharge, he had radiologic evidence of left lower pulmonary lobe atelectasis. This atelectasis never cleared and the infant required several subsequent admissions to his local hospital for pneumonia. He died 2.8 months postoperatively of pneumonia and sepsis. An autopsy was not obtained. The other late death occurred in a 9 month old girl with mongolism who had severe congestive heart failure and a pulmonary vascular resistance of 16 units·m^2 preoperatively. Her postoperative convalescence was uneventful. After discharge from the hospital, she continued to have symptoms of chronic congestive heart failure and died at home 2.9 months postoperatively after an upper respiratory infection. An autopsy performed elsewhere showed the surgical repair to be intact, but the mitral valve leaflet tissue was reported to be deficient in amount.

TABLE VII

Primary Repair of Complete Atrioventricular Canal Before Age 24 Months (1972 to October 1976): Cardiopulmonary Bypass Technique

Cardiopulmonary Bypass Technique*	Total Time (min) Mean ± SD	no.	Hospital Survivors Mean ± SD	no.	Hospital Deaths Mean ± SD	no.
Total elapsed time (min)†	85 ± 18.8	24	79 ± 21.2	14	93 ± 11.4	10
Continuous period of low flow (min)‡	31 ± 8.7	10§	29 ± 10.3	4	33 ± 8.4	6
Continuous period of circulatory arrest (min)‖	45 ± 13.0	14	43 ± 13.9	10	51 ±9.6	4

* Two patients who survived were operated on using standard hypothermic bypass and intermittent aortic cross-clamping. In one patient who did not survive a single continuous period of 20 minutes of circulatory arrest followed by 17 minutes of low flow was employed. These three patients are not included in the data presented.
† This includes time of cardiopulmonary bypass plus the period of low flow or circulatory arrest.
‡ A period of flow at 0.5 liters·min·m^2 at 20 to 26° was used instead of circulatory arrest.
§ The data are from 8 of the 10 patients. Times were not recorded in two patients, one who survived and one who died.
‖ A period of circulatory arrest at 18 to 21° was used electively for the intracardiac repair.
SD = standard deviation.

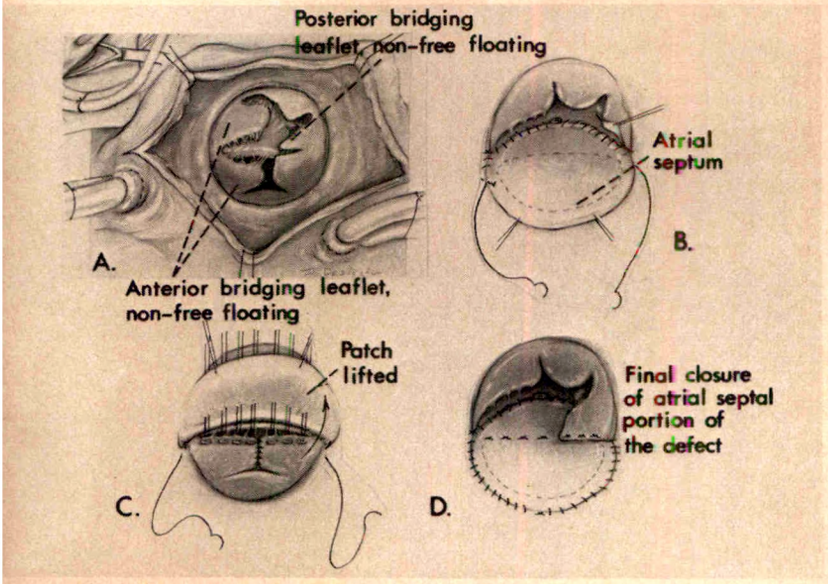


FIGURE 2. The standard repair of complete A-V canal with nonfree-floating, anterior bridging leaflet tethered by chordae to the crest of the ventricular septum and with a well developed commissure (type A, Rastelli et al.[16]) **(A).** The mitral septal (anterior) leaflet is constructed in part from valve tissue of the left ventricular side of the commissure **(B),** and its base attached to the patch **(C).** The success of this repair, the one most frequently used, depends on the adequacy of the amount of valve tissue on the left ventricular side of the commissure. The pericardial patch is attached well to the right side of the crest of the ventricular septum, to avoid the bundle of His.

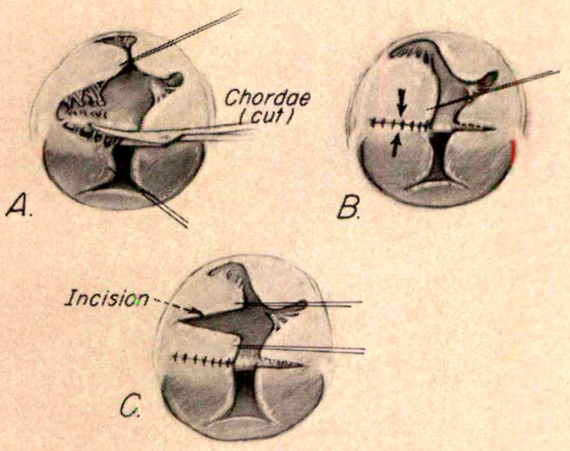


FIGURE 3. In the uncommon circumstance of atrioventricular valve tissue on the left ventricular side seeming to be insufficient in amount, the chordae of the commissure of the anterior bridging leaflet attaching to the crest of the septum are cut **(A);** the commissure is closed by interrupted 5-0 silk sutures **(B),** and a new incision **(C)** is made at the point where the patch will be placed. When necessary, a similar procedure is performed on the posterior bridging leaflet.

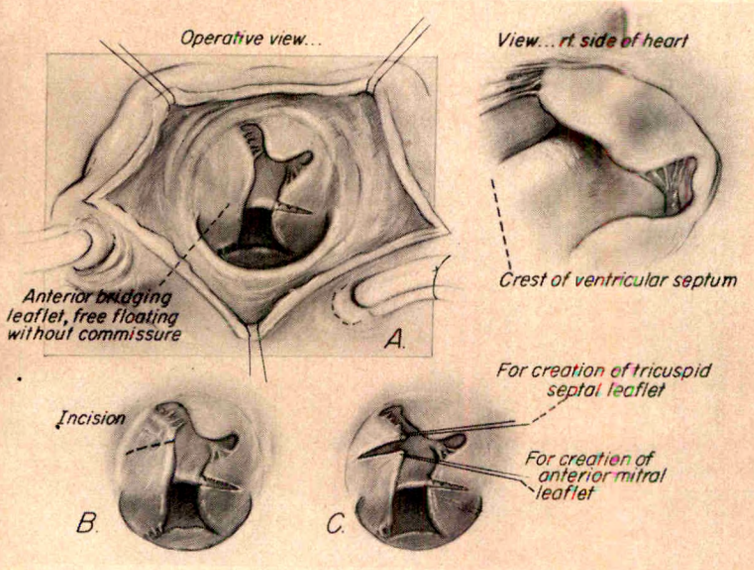


FIGURE 4. When the anterior bridging leaflet is free-floating **(A),** the incision is made eccentrically (as in **B** and **C**) when this is necessary to obtain an adequate amount of tissue to create a "mitral valve." The incision should extend to the point where the crest of the ventricular septum fuses with the atrioventricular valve ring anteriorly. Tricuspid incompetence has not resulted. rt = right.

Follow-up: The remaining 14 survivors have been followed up for a mean of 20 months (5 to 60). All have no symptoms related to the cardiac system and are normally active. Three are receiving digoxin. Eight are known to have an apical systolic murmur. None have undergone postoperative cardiac catheterization or angiocardiography.

Discussion

Complete versus intermediate and partial A-V canal: This report concerns patients with the *complete* A-V canal defect (also termed common A-V orifice).[13–16] The malformation includes an ostium primum type of atrial septal defect; a single common A-V orifice, guarded by anterior and posterior bridging leaflets that are not connected to each other and by a lateral leaflet over each ventricle; a deficiency in the ventricular septum beneath the anterior or posterior bridging leaflets, or both; and a bare area on the crest of the ventricular septum. Most patients with an *intermediate* form of A-V canal[14,15] basically require the operation performed for partial A-V canal. However, some patients with the intermediate form, whose malformation resembles the complete form, do require a complete A-V canal type of repair as did one patient in our study group. During this study period, 94 patients (one hospital death) underwent primary repair of the *partial* A-V canal defect (ostium primum type of atrial septal defect with cleft mitral anterior leaflet), including five patients (the one death noted) less than 2 years of age. These five patients are not included in this report.

We have abandoned the terms types A, B and C used by Rastelli et al.[16] to describe the bridging leaflets. Increased experience has indicated that the enormous variability of the anterior and posterior bridging leaflets, stressed by Lev and Bharati (personal communication), defies this relatively simple classification. Also, abandoning this classification has freed the surgeon to study the bridging leaflets at operation and to base his decision regarding the precise details of the repair on his findings.

Technical problems of surgical repair: The technical problems of repairing the complete A-V canal defects are much more complex than those of repairing the partial form. The modern operation for complete A-V canal was described in the early work of Maloney et al.[17] and Gerbode et al.,[18] but was clarified and refined by Rastelli and his associates.[19,20] However, infants seem to have more variability in their bridging leaflets than the patients coming to operation at an older age, who have been highly selected by natural history, and the standard operation is occasionally not applicable in its pure form in such cases. Therefore, in each patient, the valve tissue must be very carefully studied at operation to determine precisely the details of the repair. Injecting saline solution under pressure into the ventricles floats the anterior and posterior bridging leaflets and the lateral leaflets upward so that their function and competence can be studied. Then, whether the bridging leaflets are free-floating or tethered (nonfree-floating) by chordae tendineae to the crest of the ventricular septum, the repair can be tailored to the case at hand (Fig. 2, 3 and 4).

Since Lev's classic work[21] on the location of the bundle of His in complete A-V canal, the repair has been performed so as to avoid damage to the bundle. Severe residual mitral or tricuspid incompetence (except after dehiscence as described later) has not been apparent either early or late after operation, even though we have not used valve replacement in any of these patients. In one infant in this series, operated on before 1975, death occurred from severe mitral incompetence resulting from dehiscence of the newly created mitral anterior leaflet from the septal patch. The suture line creating this leaflet from portions of the anterior and posterior bridging leaflet was intact. Such dehiscences have been seen by others,[6] and the problem warrants special study.

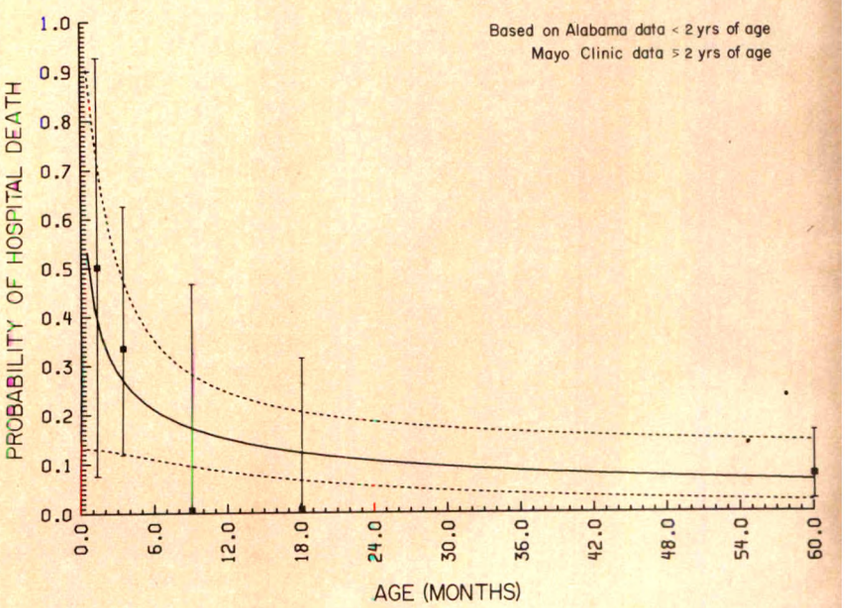


FIGURE 5. Age-specific probability of hospital death (with dotted 70 percent confidence bands), based on information from the 16 patients in the study group operated on between 1975 and October 1976 and from 27 older patients reported on by the Mayo Clinic[11] (see Methods). Logistic equation for this probability: $Pr = 1./(1. + \exp\{0.2785 \pm 1.0282 + 0.5861 \pm 0.34749[\ln (\text{age at operation})]\})$; $P_0 = 0.8$; $P_1 = 0.09$; $r_{0,1} \doteq -0.876$. Also shown are the grouped data and 70 percent confidence limits from Table II and the Mayo Clinic data centered at 60 months.

TABLE VIII

Reported Results of Palliative Pulmonary Arterial Banding for Complete Atrioventricular Canal*

Reference* Authors	Year	Patients (no.)	Hospital Deaths no.	Hospital Deaths %
Dammann et al.	1961	1	0	0
Idriss et al.	1968	15	7	47
Hunt et al.	1971	3	2	67
Horsley et al.	1970	10	3	30
Somerville et al.	1967	12	4	33
Stark et al.	1969	13	4	31
Utley	1973	10	2	20
Reid et al.	1968	2	2	100
Goldblatt et al.	1965	10	2	20
Coles et al.	1963	2	0	0
Higashino et al.	1967	6	1	17
Willman et al.	1962	3	3	100
Dooley et al.	1975	19	9	47
Oldham et al.	1972	9	1	11
Vanetti et al.	1975	5	0	0
Cayler et al.	1965	3	1	33
Newfeld et al.	1977	27	10	37
van der Horst et al.	1969	1	0	0
Cordovilla et al.	1972	2	1	50
Total		153	52	34†

* Full references to the papers included in this tabulation are available upon request.
† 70 percent confidence limits 30 to 38 percent.

Factors responsible for decreased operative mortality: We believe that the decreased hospital mortality in the infants undergoing primary repair in the recent period of 1975 to October 1976 is the result of several factors. The results of all kinds of intracardiac surgery in infants have improved in recent years, and preoperative diagnosis is more precise, allowing better preoperative planning of the operation. However, we believe that the most important factor in the improved results is improved ability to create new "mitral" and "triscuspid" valves from the anterior and posterior bridging leaflets. This improved ability is based in part on the anatomic insights of Lev and Bharati (personal communication) and on the technique of studying the common A-V valve and planning the construction of the new "mitral" and "tricuspid" valves while injecting saline solution forcefully into the ventricles. This better understanding of the repair is reflected in the mention of "deficient A-V valve tissue" in the surgeon's operative note in only 19 percent of patients (3 of 16) operated on from 1975 to 1976 compared with 64 percent of patients operated on in 1972 to 1975. We doubt that the true incidence was greater in the infants operated on in the earlier period and believe that we were less well prepared then to use properly the tissue available. The three hospital deaths in the recent group of 16 patients were all due to low cardiac output, and the present use of cold cardioplegic myocardial preservation may further improve results.

Age at operation: Although age at operation was not related to mortality in the 27 infants reported on here, and the mortality of the 16 infants operated on in 1975 and 1976 was not significantly different from that of the small number of older patients operated on by us, we are aware of the superb results in 27 older patients reported in a study from the Mayo Clinic (7 percent mortality rate, confidence limits 2 to 17 percent).[11] Using their hospital mortality data for patients more than 2 years old (which is not significantly different from our smaller experience, $P = 0.3$), and our data in 1975 and 1976 for patients less than 2 years old (which are similar to the results in smaller groups reported by Mair and McGoon[5] and by Culpepper et al.[6]), we have derived a combined probability of hospital death related to age at operation (Fig. 5). These data indicate that the risk of hospital death is greater in early infancy, but that by age 6 months it becomes similar to that in older patients.

The late results of repair of complete A-V canal in older children have been reported to be excellent in most patients who did not have severe pulmonary vascular disease preoperatively.[11] Our experience indicates that the same is true in infants. The apical systolic murmur present in 8 of our 14 surviving infants, and in 17 of the 25 older children reported on by the Mayo Clinic group,[11] may not be due to mitral incompetence. Hardesty et al.[22] demonstrated no significant mitral regurgitation on left ventriculography in three patients with a loud apical systolic murmur late after repair of complete A-V canal. Lillehei et al.[23] reported similar findings in two patients.

Clinical implications: Because of the relatively poor results (Table VIII) of pulmonary arterial banding, the only other option in infants with complete A-V canal who are so sick as to require operation in the first 6 months of life, we believe that primary repair is indicated when surgical intervention is required at this young age. The results presented here, plus the knowledge that patients with complete A-V canal often have severe pulmonary vascular disease by age 2 years[24] and that only about 20 percent of surgically untreated patients live to age 5 years (paper in preparation), indicate the wisdom of advising elective repair for patients with complete A-V canal between the ages of 1 and 2 years.

Acknowledgment

We have enjoyed the intense collaboration in these studies of Dr. L. M. Bargeron, Jr. We acknowledge the many contributions of Ms. Sandy O'Brien in preparation of tables, figures and the manuscript, and of Ms. Cathy Rohan in reviewing the literature. Mr. John Desley did the artwork.

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Differentiation of Functional and Structural Pulmonary Atresia: Role of Aortography

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Among certain critically ill neonates with severe tricuspid regurgitation, including those with Ebstein's anomaly of the tricuspid valve, tricuspid valve dysplasia, transient tricuspid regurgitation of the newborn, Uhl's anomaly and hypoplasia of the right ventricle, selective right ventriculography may not distinguish between patients with associated functional and those with structural pulmonary atresia. In patients with a normal pulmonary valve and infundibulum, functional obstruction (nonvisualization of the pulmonary artery on right ventricular angiography when the pulmonary valve is anatomically patent and nonobstructive) results from a combination of massive tricuspid insufficiency and increased perinatal pulmonary vascular resistance. This differentiation between functional and structural pulmonary atresia is essential because of the therapeutic implications.

In 33 neonates studied at cardiac catheterization from January 1974 through October 1977 standard hemodynamic measurements and right ventriculograms could not distinguish between functional and structural pulmonary atresia. Retrograde aortography, in the presence of a patent ductus arteriosus, provided excellent visualization of the pulmonary root and valve in these cases and, without exception, pulmonary regurgitation across the valve was observed in the patients with functional pulmonary atresia. Usually, the amount of regurgitated contrast material was dense, and both the right ventricle and the right atrium were opacified. In addition, among the patients with functional pulmonary atresia, the pulmonary root and valve appeared wider and more patulous than in the patients with structural pulmonary atresia, and normal or mildly increased right ventricular pressure was appreciated.

The cyanotic neonate with extreme cardiomegaly and a marked reduction in pulmonary blood flow might be anticipated to have one of several disorders.[1–12] These include (1) pulmonary atresia and intact ventricular septum with severe tricuspid regurgitation, (2) Ebstein's malformation, (3) Ebstein's malformation with pulmonary atresia, (4) isolated tricuspid valve dysplasia with severe regurgitation, (5) transient tricuspid regurgitation of the newborn, (6) hypoplasia of the right ventricle with severe tricuspid regurgitation, (7) Uhl's anomaly, or (8) combinations of these conditions.

In this group of patients, it has frequently been difficult to demonstrate angiographically unobstructed right ventricular outflow even in the presence of an anatomically nonobstructive pulmonary valve or infundibulum.[1,4] This clinical differentiation between functional and structural right ventricular outflow tract obstruction is of considerably more than academic interest because of the differences in management of these often critically ill neonates. In this study we report on the role of aortography in making this differentiation.

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TABLE I

Types of Congenital Heart Disease Requiring Differentiation of Functional and Organic Pulmonary Atresia

Congenital Heart Defect*	Patients Studied (no.)
Ebstein's malformation	9
Pulmonary atresia, intact ventricular septum, severe tricuspid regurgitation and subsystemic right ventricular pressure	8
Ebstein's malformation with pulmonary atresia	3
Isolated tricuspid valve dysplasia	3
Isolated right ventricular hypoplasia with severe tricuspid regurgitation	3
Transient tricuspid regurgitation of the newborn	3
Two or more of the above conditions	4
Total	33

* Proved at necropsy or surgical exploration (at time of tricuspid anuloplasty or replacement) or assessed from clinical course.

Patients

The dilemma of differentiating functional from structural pulmonary atresia was raised in 33 infants less than 1 week of age, studied clinically and with cardiac catheterization and angiocardiography at this center between January 1974 through October 1977. During this interval, 3,032 patients underwent cardiac catheterization and angiocardiography at our institution. The type of defect and distribution of these 33 patients are presented in Table I. All 33 patients had undergone biplane anteroposterior and lateral right ventricular cineangiocardiography, and satisfactory biplane aortograms were also available for review in all but 4. These four patients had technically unsatisfactory aortograms, but biplane left ventricular cineangiocardiograms, with visualization of the aortic arch and the ductus arteriosus, were available for study. The anatomic diagnosis in the 33 cases was confirmed either at necropsy or surgical exploration in 25 infants. In the remaining eight patients not subjected to surgical intervention, gradual improvement in clinical status and in partial pressure of oxygen (PO_2) was interpreted as consistent with resolution of the functional pulmonary atresia. In an additional 30 patients with the typical clinical, hemodynamic and angiocardiographic features of organic pulmonary atresia and intact ventricular septum, biplane right ventriculograms and aortograms were reviewed for comparison with those of the study group.

The right ventriculograms and aortograms were obtained using 1.0 to 1.5 cc of contrast agent per kilogram body weight, injected at flow rates of 4 to 10 cc/sec; 35 mm cineangiograms of the right ventricle were obtained in standard anteroposterior and lateral projections; aortography was performed in either the left anterior oblique or the anteroposterior and lateral projections. Right ventriculograms were obtained using standard angiographic or flow-directed catheters, and the aortograms were obtained using no. 5F umbilical arterial catheters.

Findings

Right ventriculograms: All 33 patients had severe cardiomegaly (Fig. 1). The right ventricular angiographic features have been thoroughly documented in these patients, and our findings are consistent with these reports.[1–11,13–20]

In brief, selective right ventriculograms demonstrated severe tricuspid regurgitation into the right atrium, irrespective of the pathologic nature of the tricuspid valve (Fig. 2 to 5). The right atrium occupied most of the right hemithorax in the cases studied. In neither the anteroposterior or the lateral projection of the right ventriculograms was contrast material seen to pass from the right ventricle into the pulmonary artery. Contrast material was ejected by way of the regurgitant tricuspid valve into the right atrium, with subsequent right to left shunting at the atrial level and opacification of the left heart chambers. From the right ventriculogram alone, pulmonary atresia, either functional or structural, in concert with some form of tricuspid valve disease was diagnosed in each case.

The lateral projection of the right ventriculograms revealed a very patulous distal infundibulum in most of the patients with functional pulmonary atresia (Fig. 3 and 4). Similarly, in the patients with structural pulmonary atresia and normal or mildly elevated right ventricular pressure, the right ventricular infundibulum was often very dilated (Fig. 6) and indistinguishable from that of the patient with functional pulmonary atresia. If the infundibulum was significantly underdeveloped, in conjunction with a small right ventricular cavity, these findings were interpreted as more consistent with structural than with functional pulmonary atresia.

Role of aortography in differentiating between functional and structural pulmonary atresia: A technically satisfactory aortogram (in the presence of a patent ductus arteriosus) demonstrated sequentially opacification of the ductus arteriosus and the main and branch pulmonary arteries. With functional pulmonary atresia, contrast material regurgitated across the pulmonary valve into the right ventricle and right atrium and, in some patients, contrast material could be visualized refluxing into the hepatic veins and superior vena cava (Fig. 2 to 4). Among the patients with functional pulmonary atresia, the pulmonary valve ring and sinuses of Valsalva appeared angiocardiographically of normal size or even patulous. With the cineangiocardiographic technique, little motion of the pulmonary valve was appreciated. It was difficult to ascertain if the pulmonary valve of these patients was thickened. Frequently, the regurgitated contrast material "jetted" from pulmonary artery into the distal right ventricular infundibulum. Selective left ventriculography in four patients with functional pulmonary atresia demonstrated passage of contrast material across the ductus arteriosus, and then into the pulmonary artery, right ventricle and right atrium.

With structural pulmonary atresia, the pulmonary root varied from markedly underdeveloped to normal in size (Fig. 6). The main and branch pulmonary arteries were significantly underdeveloped in about 30 percent of our patients. Among some patients with hemodynamic and right ventricular angiographic evidence of organic pulmonary atresia, aortography in the presence of a patent ductus arteriosus demonstrated a trace of regurgitation from the pulmonary artery to the right ventricular infundibulum. The amount of regurgitated contrast material was extremely small and was certainly insignificant when compared with that among most of the patients with functional pulmonary atresia. This finding obviously suggests critical pulmonary stenosis rather than the atresia indicated in the biplane right ventriculogram.

Hemodynamic findings: In brief, the hemodynamic measurements were not helpful in differentiating functional from structural pulmonary atresia among these 33 patients. No separation could be made on the basis of atrial pressures or wave forms. Among the neonates with functional pulmo-

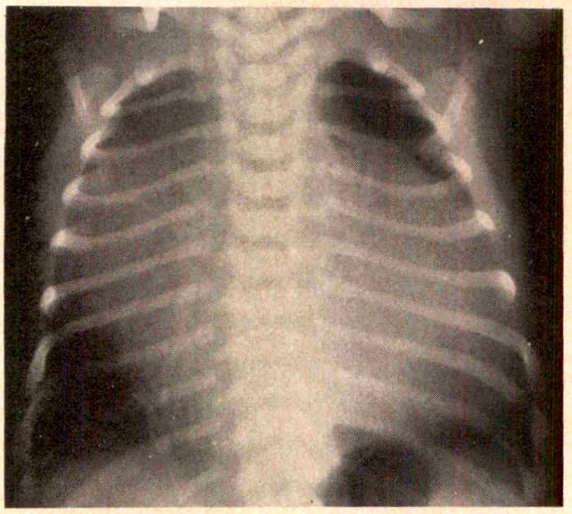
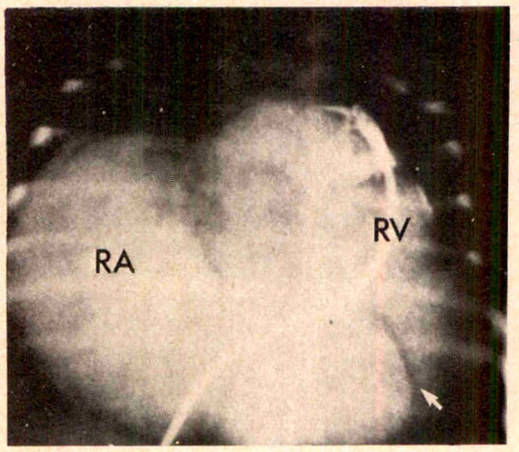
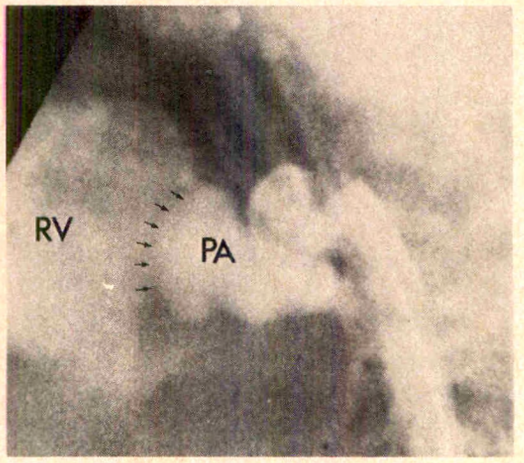
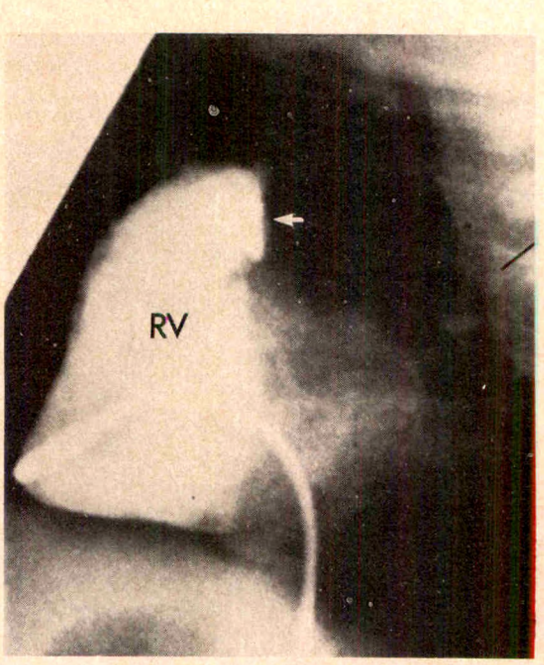


FIGURE 1 (left). Chest radiograph (anteroposterior projection) from a neonate with Ebstein's anomaly of the tricuspid valve and functional pulmonary atresia. This radiograph is typical of the neonate with functional pulmonary atresia. The heart is huge and obscures the lung fields. The pulmonary blood flow is greatly reduced.

FIGURE 2 (bottom). Selective right ventriculogram **(left)** and lateral aortogram **(right)** from a neonate with severe Ebstein's anomaly and functional pulmonary atresia. **Left,** the cardiac silhouette is huge. There is regurgitation of contrast material from the right ventricle (RV) into the right atrium (RA). The displaced tricuspid leaflet is also demonstrated **(white arrow). Right,** the lateral aortogram demonstrates a normal-sized main pulmonary artery (PA) with regurgitation of contrast material across the pulmonary valve **(black arrows)** into a dilated right ventricular infundibulum. Necropsy demonstrated Ebstein's anomaly of the tricuspid valve, marked right atrial dilatation and a dilated pulmonary infundibulum. The pulmonary valve was dysplastic but not obstructive.







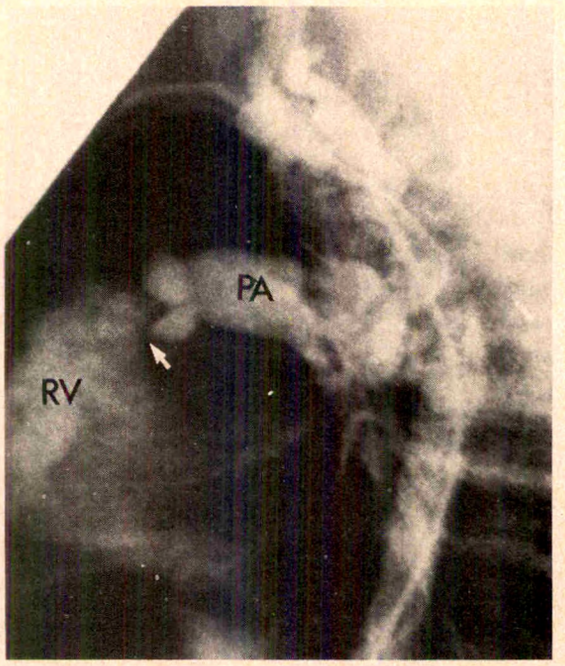


FIGURE 3. Lateral right ventricular cineangiocardiogram **(left)** and lateral aortogram **(right)** in a patient with Ebstein's anomaly and functional pulmonary atresia. **Left,** the distal infundibulum is quite dilated, and no anterograde flow into the pulmonary arteries is appreciated **(arrow). Right,** lateral aortogram performed after the patient had been given intraarterial prostaglandin. The pulmonary artery (PA) and pulmonary root **(arrow)** are clearly visualized. There is free regurgitation of contrast material into the right ventricle (RV).

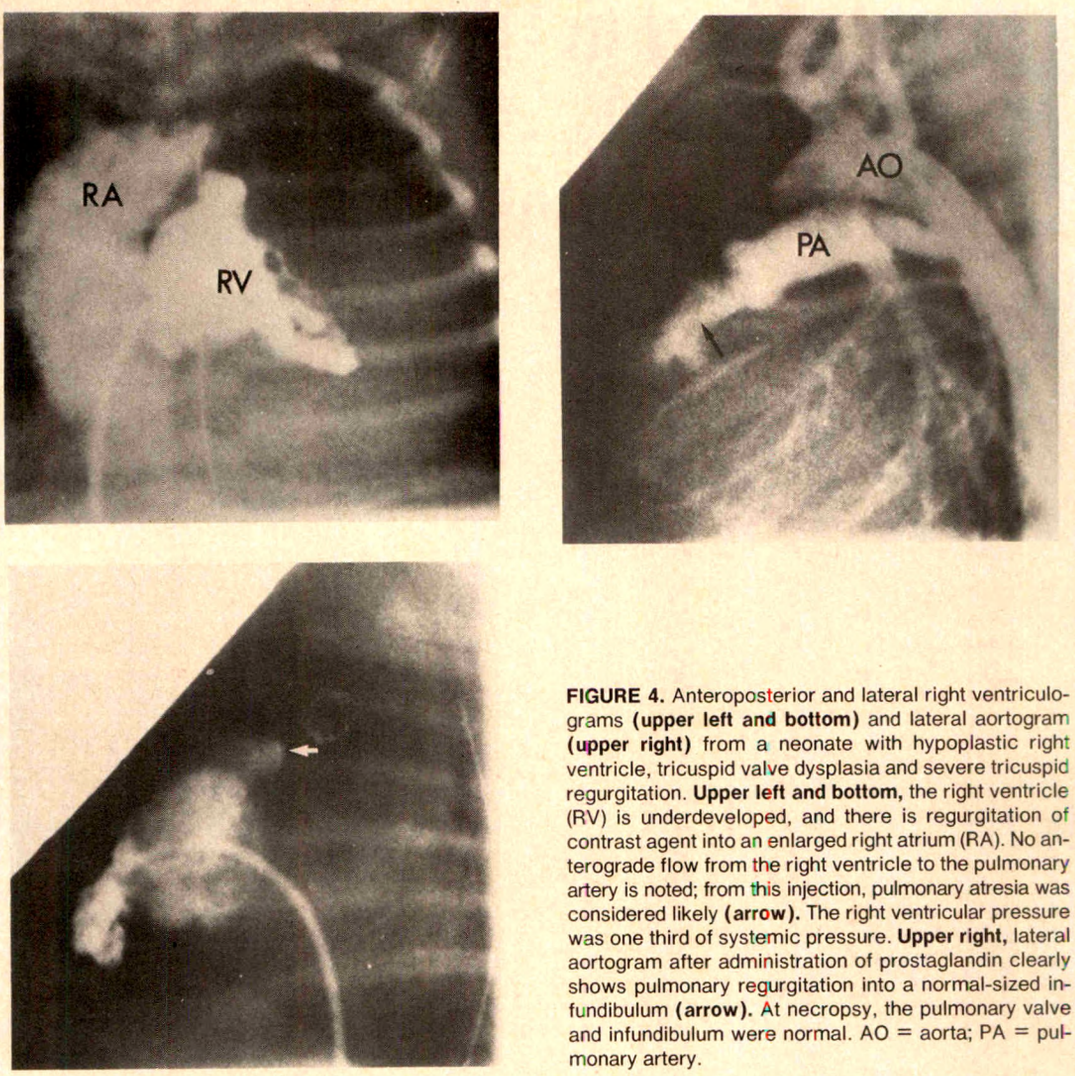


FIGURE 4. Anteroposterior and lateral right ventriculograms **(upper left and bottom)** and lateral aortogram **(upper right)** from a neonate with hypoplastic right ventricle, tricuspid valve dysplasia and severe tricuspid regurgitation. **Upper left and bottom,** the right ventricle (RV) is underdeveloped, and there is regurgitation of contrast agent into an enlarged right atrium (RA). No anterograde flow from the right ventricle to the pulmonary artery is noted; from this injection, pulmonary atresia was considered likely **(arrow).** The right ventricular pressure was one third of systemic pressure. **Upper right,** lateral aortogram after administration of prostaglandin clearly shows pulmonary regurgitation into a normal-sized infundibulum **(arrow).** At necropsy, the pulmonary valve and infundibulum were normal. AO = aorta; PA = pulmonary artery.

nary atresia, right ventricular systolic pressure ranged from normal to systemic but was not greater than systemic pressure in any case. Right ventricular pressure among this group of patients generally ranged from one third to three fourths of systemic pressure. Similarly, the right ventricular pressure of the infants with organic pulmonary atresia and extreme cardiomegaly ranged from normal to greater than systemic but was usually less than systemic pressure. In contrast, in patients with organic pulmonary atresia and mild to moderate cardiomegaly, systemic, and often suprasystemic, right ventricular pressure was recorded.

Presence of right ventricular myocardial sinusoidal-coronary arterial communications: The pathologic and angiocardiographic features of these communications in patients with pulmonary atresia and intact ventricular septum have been extensively documented.[1,4,15–17,19,21,22,23–26] These findings were not noted in any patient with functional pulmonary atresia and were found in only one patient with structural pulmonary atresia and subsystemic right ventricular pressure. These communications have been estimated to be present in 10 to 40 percent of patients with structural pulmonary atresia and systemic or suprasystemic right ventricular pressure. Thus, their presence should be interpreted as consistent with structural, rather than functional, pulmonary atresia.

Discussion

The classic angiocardiographic features of structural pulmonary atresia and intact ventricular septum have been thoroughly reported, and this diagnosis usually poses no difficulty.[1,2,4,7,13–17,22–24] However, in one group of neonates it may be extremely difficult to differentiate functional from structural pulmonary atresia.[1,2,4,6,9,11] Functional pulmonary valve obstruction has been demonstrated angiocardiographically among neonates with grossly ineffective forward ejection of right ventricular blood. This results from a combination of massive tricuspid insufficiency and an elevated perinatal pulmonary vascular resistance.[1,3,4] Obviously, anatomic pulmonary atresia can be excluded by catheter passage or by angiographic demonstration of direct entry contrast medium into the pulmonary artery from the right ventricle. However, in patients with functional rather than anatomic pulmonary atresia, the combination of severe tricuspid regurgitation and pulmonary regurgitation frequently may make it difficult if not impossible to probe the pulmonary artery with either a standard or a flow-directed catheter.

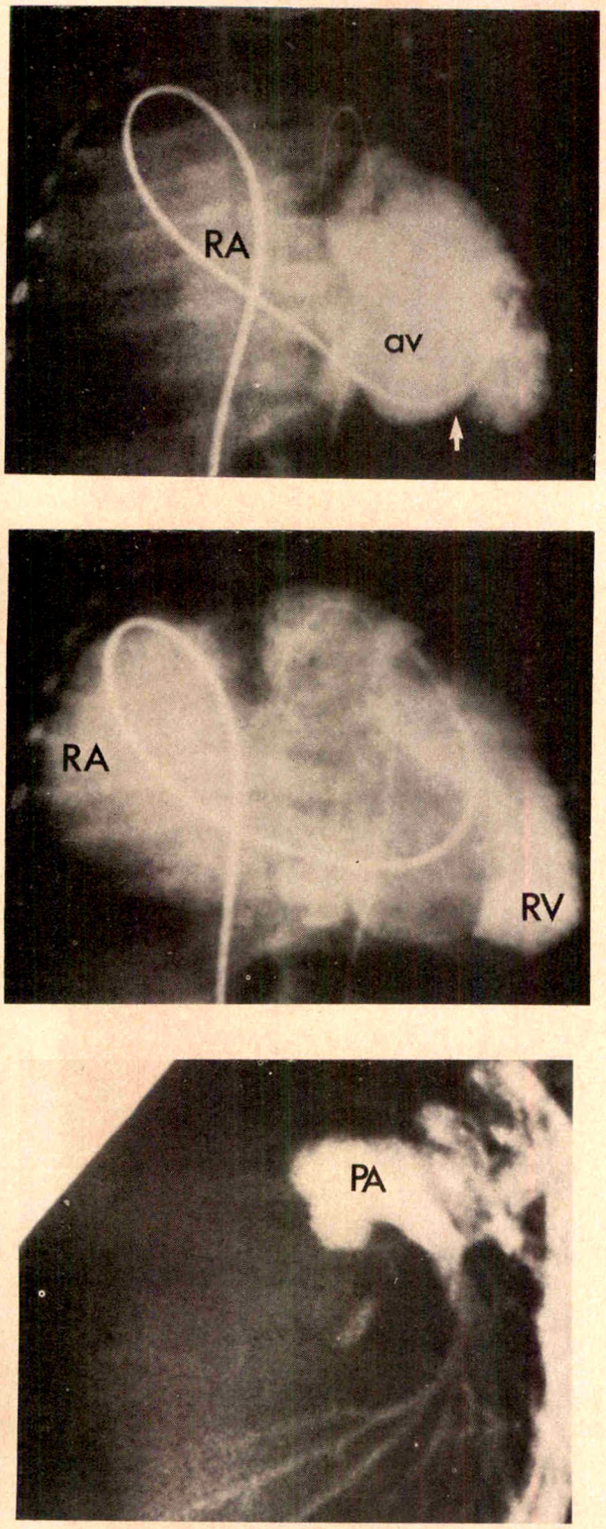


FIGURE 5. Anteroposterior right ventricular cineangiocardiograms **(top and center)** and lateral aortogram **(bottom)** from a neonate with severe Ebstein's anomaly. Same patient as in Figure 1. **Top,** there is no anterograde flow into the pulmonary artery. Both the notch of the displaced tricuspid valve **(white arrow)** and the atrialized portion of the right ventricle (av) are clearly visualized. RA = right atrium. **Center,** the later frame shows severe tricuspid regurgitation into the gigantic right atrium. RV = right ventricle. **Bottom,** in the lateral aortogram, the pulmonary root appears normal or perhaps mildly enlarged. The sinuses of Valsalva are clearly visualized. This frame does not demonstrate pulmonary regurgitation. PA = pulmonary artery.

TABLE II

Features Observed in Patients With Functional or Organic Pulmonary Atresia

	Functional	Organic
Massive cardiomegaly	+	+
Tricuspid regurgitation		
Severe	+	+
Transient	Occasionally	0
Right ventricular cavity		
Normal or enlarged	+	+
Underdeveloped	+	+
Dilated right ventricular infundibulum	+	+
Significantly narrowed right ventricular infundibulum	0	+
Suprasystemic right ventricular pressure	0	+
Subsystemic right ventricular pressure	+	+
Myocardial sinusoidal-coronary arterial communications	−	+
Significant pulmonary regurgitation into the right ventricle and right atrium on aortography	+	−
Faint pulmonary regurgitation into the distal right ventricular infundibulum on aortography	Rarely	Occasionally with critical pulmonary stenosis
Ductal-dependent pulmonary blood flow	+	+

+ = present; − = absent or very uncommon.

Role of aortography in study of pulmonary valve: Although we have not found hemodynamic data to be helpful in the differentiation of functional from structural pulmonary atresia, we have been impressed with the efficacy of aortography as a method of retrograde visualization of the pulmonary root and demonstration of pulmonary valve patency among neonates with functional pulmonary atresia. This approach, of course, necessitates patency of the ductus arteriosus. In the neonate, aortography has been accomplished either with the umbilical arterial approach or with use of a flow-directed venous catheter positioned in the ascending aorta.[27,28] If the ductus arteriosus is significantly narrowed as reflected in the arterial PO_2, the intraarterial (or venous) administration of an E-type prostaglandin before aortography may afford better visualization of the pulmonary root and valve and improve tissue oxygenation.[29–32]

Visualization of the pulmonary root with aortography in 29 patients and left ventriculography has allowed us to make the distinction between functional and structural pulmonary atresia. In one patient, a newborn with Ebstein's anomaly and massive cardiomegaly (Fig. 5), only very faint regurgitation across the pulmonary valve was demonstrated but, in conjunction with a very wide pulmonary valve anulus, we interpreted these findings as consistent with functional pulmonary atresia. At necropsy, this patient had a normal pulmonary valve and very severe Ebstein's anomaly of the tricuspid valve.

Features of functional versus organic pulmonary atresia: Pulmonary valve regurgitation as visualized on aortography does not ensure a nonobstructive pulmonary valve. Rarely, aortography has demonstrated regurgitation across a severely stenotic pulmonary valve.

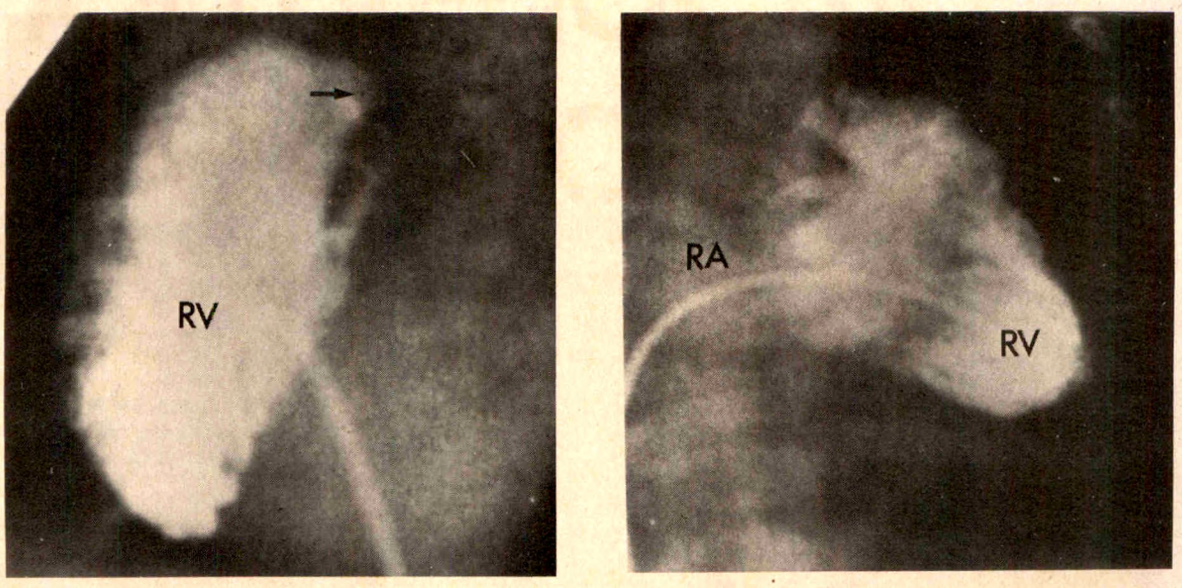


FIGURE 6. Selective biplane anteroposterior **(left)** and lateral **(right)** right ventriculograms from a neonate with structural pulmonary atresia, mildly elevated right ventricular pressure and severe tricuspid regurgitation. The right ventricle (RV) is enlarged, and the right ventricular infundibulum is patulous. The distal infundibulum has narrowed slightly, and there is pulmonary atresia **(arrow).** The right atrium (RA) is faintly opacified in this frame. The diagnosis was confirmed at surgery.

We have observed this both in patients with systemic (or suprasystemic) and in those with subsystemic right ventricular pressure. In the patient with severe organic pulmonary obstruction and pulmonary regurgitation, the pulmonary root usually, but not invariably, appears considerably narrowed, especially compared with the angiographic appearance of the pulmonary root with functional pulmonary atresia. Indeed, in patients with structural pulmonary atresia, the pulmonary root can appear entirely normal in size.[7] However, significant pulmonary regurgitation (as assessed from opacification of the inflow portion of the right ventricle and the right atrium) has not been observed in any patient with severe structural pulmonary stenosis. Table II outlines the features common to both functional and structural pulmonary atresia, and includes items that may be helpful in differentiating them.

In patients with functional pulmonary atresia, the mechanism of regurgitation of contrast material (and presumably blood) across the pulmonary valve is uncertain. Among some of our necropsy patients with functional pulmonary atresia, the pulmonary valve leaflets appeared entirely normal, whereas in others, they appeared to be somewhat dysplastic or redundant. In one patient, the valve was congenitally bicuspid but was not obstructive. The pulmonary infundibulum among the patients with functional pulmonary atresia appears widely dilated and patulous and, in addition, the pulmonary valve ring is normal or dilated. Our cineangiocardiographic data suggest that pulmonary regurgitation occurs during the late phase of right ventricular systole or early diastole.

Role of prostaglandin infusion in diagnosis and palliation: Both groups of patients may be significantly hypoxic, and pulmonary blood flow may be entirely ductal-dependent. Indeed, short-term palliation may be afforded by prostaglandin infusion before, during and after diagnostic cardiac catheterization.[29–32] With regression of the elevated perinatal pulmonary vascular resistance, it is hoped that the infant with functional pulmonary atresia would sustain some anterograde pulmonary blood flow and show gradual clinical improvement. Nearly half of our patients were studied angiocardiographically without the benefit of prostaglandin infusion. Indeed, our observations on the role of aortography in the differentiation of structural from functional pulmonary atresia were made before Olley et al. instituted the clinical use of prostaglandin in this institution. We now recognize that administration of prostaglandin in these infants has two advantages: (1) It allows better tissue oxygenation, and (2) it should allow better visualization of the pulmonary root and hence the presence or absence of reflux of contrast material across the pulmonary valve. In those infants with functional pulmonary atresia and extreme tricuspid regurgitation, both the medical and surgical prognosis must be guarded. Finally, we hope that aortography might obviate unnecessary exploratory thoracotomy in most patients with functional pulmonary atresia.

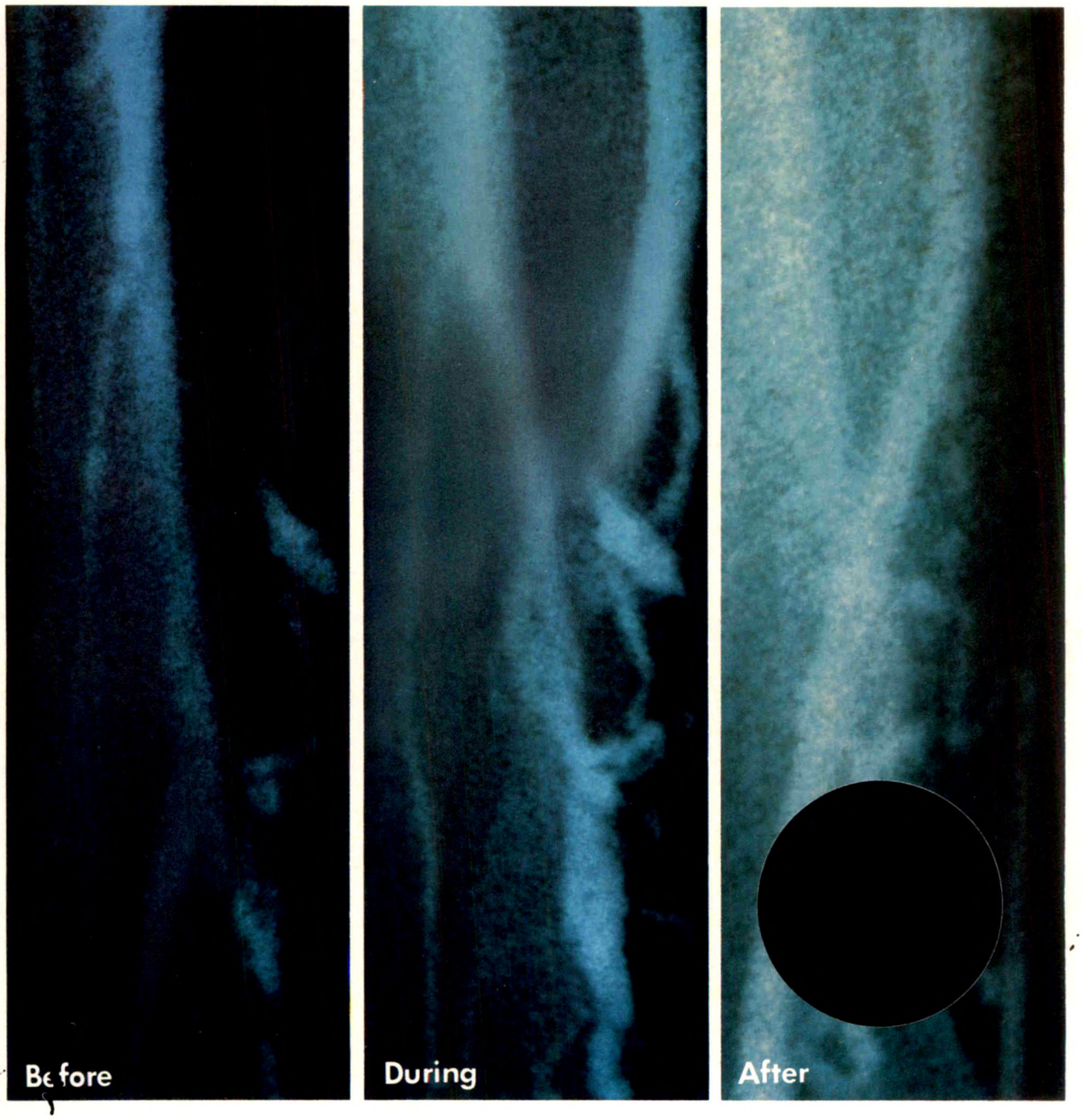
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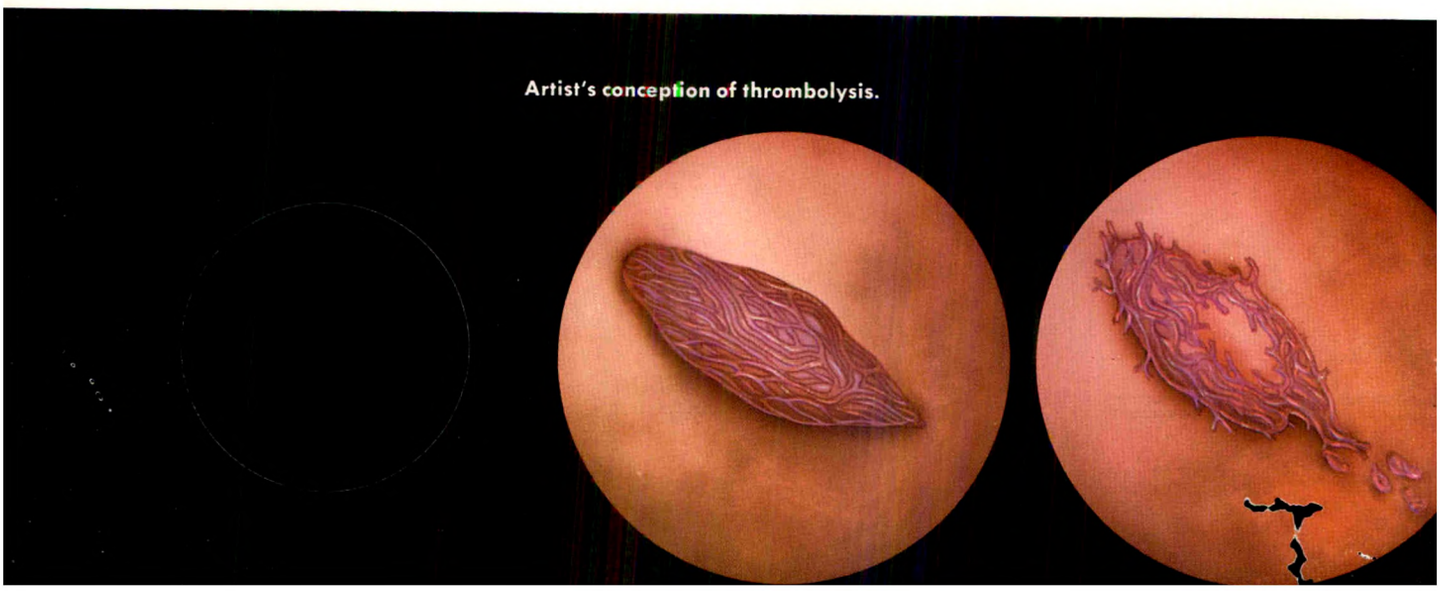
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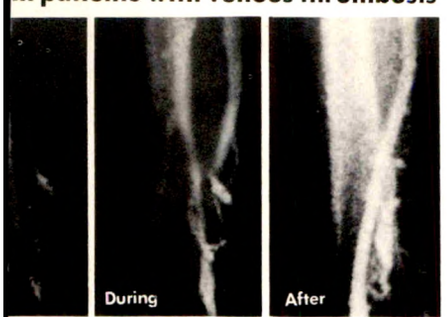
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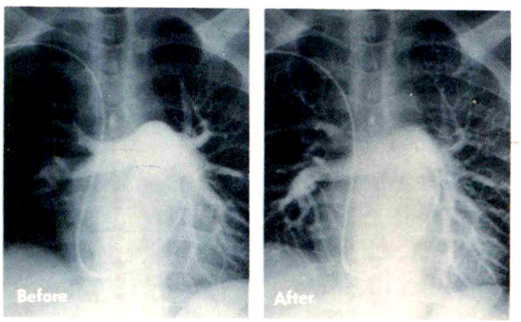
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Table I
Comparative angiographic results during controlled investigations*

Results	Venous Thrombosis		Pulmonary Embolism	
	Streptase (37 patients)	Heparin (41 patients)	Streptase (36 patients)	Heparin (88 patients)
Complete clearing	22%	5%	22%	5%
Significant, but incomplete, clearing	32%	2%	44%	6%
Minimal clearing	21%	20%	20%	43%
No change	22%	66%	14%	35%
Worse	3%	7%	0%	11%

In most cases, clearance was achieved in 72 hours or less.

For best results, Streptase should be used within 2 weeks after onset of venous thrombosis symptoms and within 5 days after onset of pulmonary embolism symptoms. Please see last page of this advertisement for a brief summary of prescribing information.

*Data on file and available on request from Hoechst-Roussel Pharmaceuticals Incorporated. Pulmonary embolism data include those taken from National Heart and Lung Institute study.

Thrombosis and thrombolysis information available

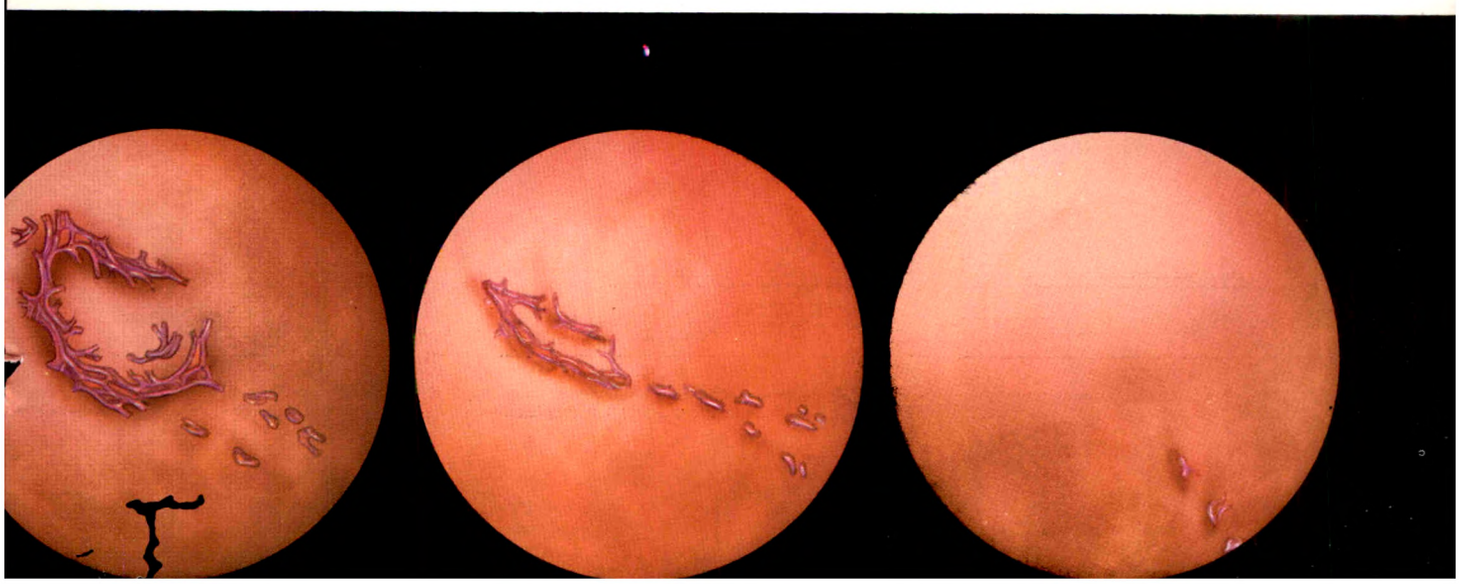
When considering the use of Streptase (streptokinase), comprehensive knowledge of prescribing information and strict observance of the contraindications, warnings, precautions, and dosage and administration instructions are most important to minimize the incidence and severity of adverse reactions, the most significant and frequent being fever, allergy and bleeding. Use of Streptase requires an interdisciplinary effort and therefore should be reserved for those hospitals with facilities for angiography, coagulation testing and volumetric or syringe pump administration of Streptase intravenously.

Hoechst-Roussel has prepared a comprehensive educational program on thrombosis and thrombolysis that includes two films, associated monographs, dosage and administration guidelines and a Speakers Bureau of physicians experienced in the use of thrombolytic therapy.

For information, interested physicians may contact Scientific Services, Room 236, Building M, Hoechst-Roussel Pharmaceuticals Inc., Somerville, New Jersey 08876, (201) 685-2611, or the local Hoechst-Roussel Sales Representative.

For a complete list of indications, contraindications, warnings, precautions, adverse reactions and dosage information, please refer to the full prescribing information for Streptase, a summary of which appears on the following page.

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Streptase®
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Brief Summary of the Prescribing Information

Streptase® (streptokinase) should only be used by physicians with wide experience in the management of thrombotic disease in hospitals where the recommended clinical and laboratory monitoring can be performed. The full prescribing information should be read for complete details.

When considering treatment with Streptase® (streptokinase) the overall clinical status and history of the patient should be carefully assessed. The hemostatic capability of the patient is more profoundly altered and bleeding more frequent with Streptase® (streptokinase) therapy than with heparin or oral coumarin compound anticoagulant therapy. When bleeding occurs it is also more severe and more difficult to manage. The potential risk of serious hemorrhage relative to such factors as age, physical condition, and underlying bleeding tendency of the patient should be weighed against the potential benefits of treating the patient with Streptase® (streptokinase).

Indications

Pulmonary Embolism: Streptase® (streptokinase) is indicated in adults for the lysis of acute massive pulmonary emboli, defined as obstruction or significant filling defects involving two or more lobar pulmonary arteries or an equivalent amount of emboli in other vessels. It may also be indicated for embolization accompanied by unstable hemodynamics. The diagnosis should be confirmed by objective means. Streptase® (streptokinase) treatment should be instituted as soon as possible after onset of symptoms and no later than five days after onset. Reduction of morbidity or mortality has not been established.

Deep Vein Thrombosis: Streptase® (streptokinase) is indicated for lysis of acute, extensive thrombi of the deep veins in adults. Diagnosis should be confirmed by objective methods.

Streptase® (streptokinase) should be administered as soon as possible after the onset of the thrombotic event (preferably within several days), although slight enhancement of clot lysis has been shown with initiation of therapy up to two weeks after the onset of symptoms.

Contraindications

Predisposition to Bleeding: Because thrombolytic therapy increases the risk of bleeding, Streptase® (streptokinase) is contraindicated when the following conditions exist: surgery within 10 days, liver or kidney biopsy within 10 days, intraarterial diagnostic procedure within 10 days, ulcerative wound, recent trauma, visceral carcinoma, parturition (within 10 days), ulcerative colitis or diverticulitis, hypertension, liver or kidney disease, thrombocytopenia or other evidence of defective hemostasis, active tuberculosis, subacute bacterial endocarditis, gastrointestinal bleeding within 6 months.

Predisposition to Allergy: Streptase® (streptokinase) is contraindicated in patients with a history of a previous severe allergic reaction to Streptase® (streptokinase) or who present a significant risk of an allergic response.

Recent Cerebral Embolism, Thrombosis, or Hemorrhage: Treatment with Streptase® (streptokinase) is contraindicated for at least two months.

Predisposition to Systemic Infection: Use of Streptase® (streptokinase) in septic thrombophlebitis may be hazardous because of the risk of inducing systemic infection.

Warnings

Bleeding: Activation of the fibrinolytic system with Streptase® (streptokinase) results in a more profound alteration of the hemostatic status of the patient than does anticoagulant therapy. Although the aim of Streptase® (streptokinase) therapy is the production of sufficient amounts of plasmin for lysis of intravascular deposits of fibrin, other fibrin deposits are also destined for lysis and bleeding may result. The possibility of bruising or hematoma formation especially with intramuscular injections is high.

Bleeding at sites of recent invasive procedures may occur. Should an arterial puncture be *absolutely* necessary, the femoral artery must be avoided and the radial or brachial artery used. Also, invasive venous procedures should be performed as carefully and infrequently as possible. If the bleeding from an invasive site is not serious, treatment may be continued with appropriate clinical observations.

Spontaneous bleeding from internal sites may also occur.

Should serious spontaneous bleeding occur, the infusion of Streptase® (streptokinase) should be terminated immediately.

In addition to its fibrinolytic action, plasmin also degrades fibrinogen, Factor V, Factor VIII, and other proteins. These products possess an anticoagulant effect and should be monitored by serial thrombin time determinations.

Predisposition to Cerebral Embolism: Treatment with Streptase® (streptokinase) of patients with conditions in which there is possible risk of cerebral embolism may be hazardous because of the risk of bleeding into the infarcted area.

Allergy: Streptase® (streptokinase) is antigenic, thus, allergic reactions including anaphylaxis may occur.

Recipients of Streptase® (streptokinase) should be observed carefully during the first few hours of therapy. Patients with known allergies to other antigens are more likely to react. If significant changes in blood pressure or asthmatic symptoms occur which might be due to allergy, the infusion should be terminated and symptomatic treatment employed.

Other mild allergic manifestations have also been observed but generally are not serious enough to require discontinuation of therapy.

Use of Anticoagulants: Concurrent use of anticoagulants with Streptase® (streptokinase) is not recommended and may be hazardous. A thrombin time of less than twice the normal control value is adequate for starting Streptase® (streptokinase) infusions safely following the use of heparin. Heparin should not be started following Streptase® (streptokinase) therapy until the thrombin time has returned to less than twice the normal control value.

In order to minimize rethrombosis, the use of intravenous heparin followed by oral anticoagulant therapy is considered a necessary adjunct following Streptase® (streptokinase) therapy.

Use in Pregnancy and in Children: Streptase® (streptokinase) therapy during pregnancy and in children is not recommended.

Precautions

If the patient's history gives rise to suspicion of elevated resistance, the streptokinase resistance test should be used to determine the proper loading dose. When resistance levels in excess of 1,000,000 I.U. are found, Streptase® (streptokinase) should not be administered.

Streptase® (streptokinase) infusions have been associated with altered platelet function. Concurrent use of drugs that may potentiate this effect should be avoided.

Adverse Reactions

Incidence and Management

Bleeding: Severe spontaneous bleeding has been documented in 6 of 292 patients during Streptase® (streptokinase) treatment. Several fatalities due to cerebral hemorrhage have occurred during Streptase® (streptokinase) therapy. Less severe spontaneous bleeding has been observed during Streptase® (streptokinase) treatment at approximately twice the frequency as that occurring during heparin therapy. In several instances, spontaneous bleeding has been traced to concomitant anticoagulant treatment which is not recommended.

Management of Severe Bleeding: Streptase® (streptokinase) therapy must be discontinued. If very rapid reversal of the fibrinolytic state is required, treatment with aminocaproic acid (EACA) can be instituted.

Plasma volume expanders are indicated to replace blood volume deficit. If blood loss has been large, Red Blood Cells (Human) may also be indicated. If only Whole Blood (Human) is available, it may also be used.

Allergic Reaction

Incidence: Reactions determined to represent possible anaphylaxis have been observed in 7 of 292 patients treated with Streptase® (streptokinase). These ranged in severity from minor breathing difficulty to bronchospasm, periorbital swelling, or angioneurotic edema. Other milder allergic effects have been observed in approximately 12% of patients. There was no apparent relationship to dosage.

Management of Allergic Reactions: Mild and moderate reactions may be managed with concomitant antihistamine and/or corticosteroid therapy. Severe allergic reactions require immediate discontinuation of Streptase® (streptokinase), with corticosteroids administered intravenously as required.

Fever

Incidence: One-third of patients treated with Streptase® (streptokinase) have shown increases in body temperature of 1.5°F or more; the incidence of fever ≥104°F was 3.4%.

Management: Symptomatic treatment is usually sufficient to alleviate discomfort. The use of acetaminophen rather than aspirin is recommended.

Phlebitis: Phlebitis near the site of intravenous infusion of Streptase® (streptokinase) has occurred in less than 2% of patients.

How Supplied

Streptase® (streptokinase) is supplied as a lyophilized white powder in 6.5 ml vials (in packages of 10) with color-coded labels corresponding to the amount of purified Streptase® (streptokinase) in each vial as follows: 100,000 IU (yellow), 250,000 IU (green), 750,000 IU (blu

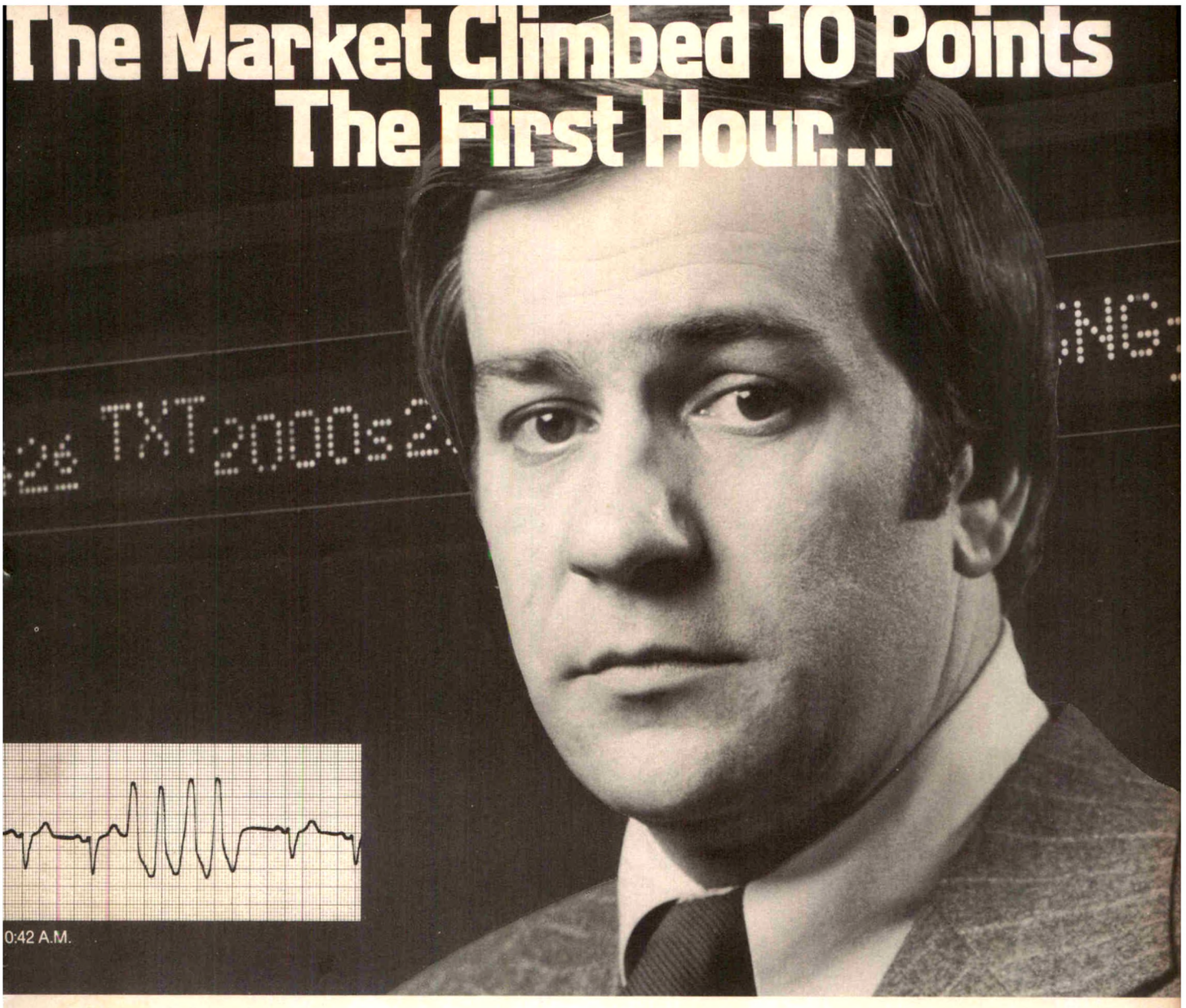
In each vial there is a 20% overfill above that stated on the label. Each vial also contains 25 mg cross-linked gelatin polypeptides and 25 mg sodium L-glutamate as stabilizers.

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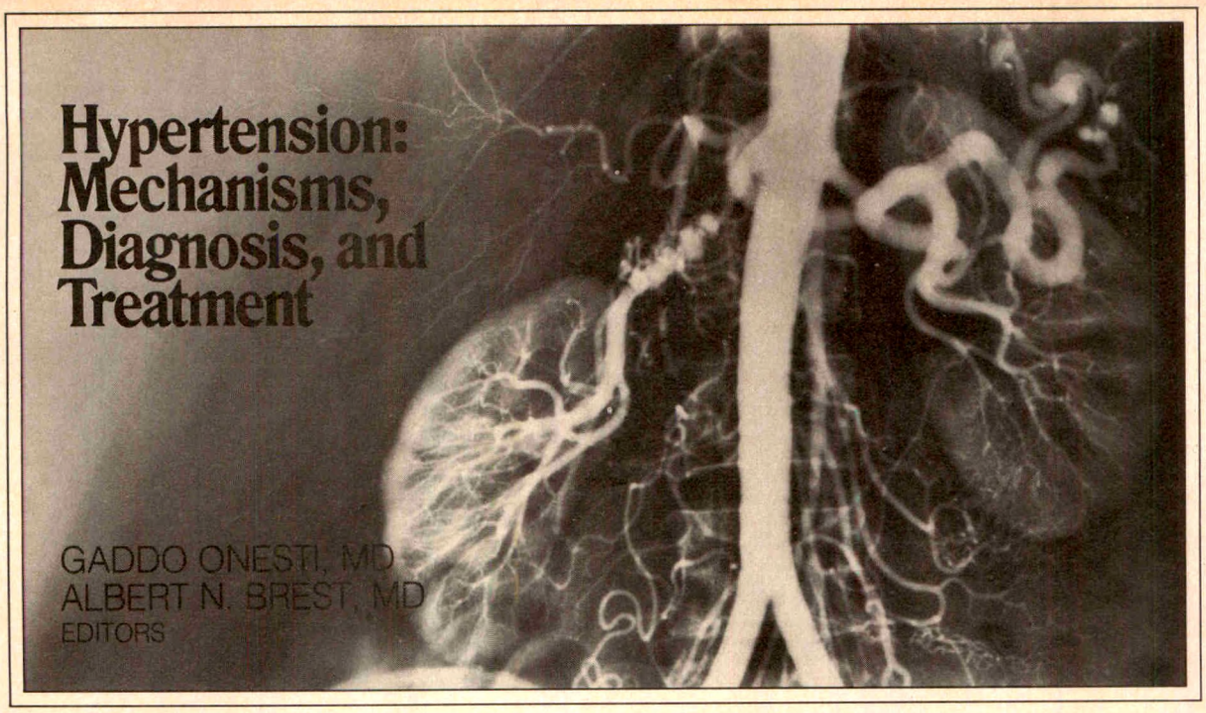
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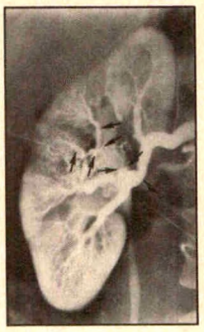


AN IMPORTANT NEW ADDITION TO THE CARDIOVASCULAR CLINICS SERIES.

VOLUME 9 NUMBER 1 — ALBERT N. BREST, MD, EDITOR IN CHIEF

Edited by **Gaddo Onesti, MD,** Guest Editor, Professor of Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania; and **Albert N. Brest, MD,** Professor of Medicine and Head of the Division of Cardiology, Jefferson Medical College and Hospital, Philadelphia, Pennsylvania.

About 415 pp/116 illus. (1978) $35.00



An authoritative new work, this new volume offers a current and practical assessment in the diagnosis and management of the various forms of hypertension. Recent advances in hypertension are considered from the physiologic, diagnostic and therapeutic aspects. Particular attention is given to the renin-angiotensin system, high blood pressure in children and the importance of systolic hypertension, as well as drug treatment of the ambulatory patient and hypertensive emergencies. Twenty-two chapters written by recognized authorities in the field provide an up-to-date account of the complexities of this disease. This new addition to the Cardiovascular Clinics Series is an important reference book not only for cardiologists, internists, but for those interested in renal disease and hypertension during pregnancy.

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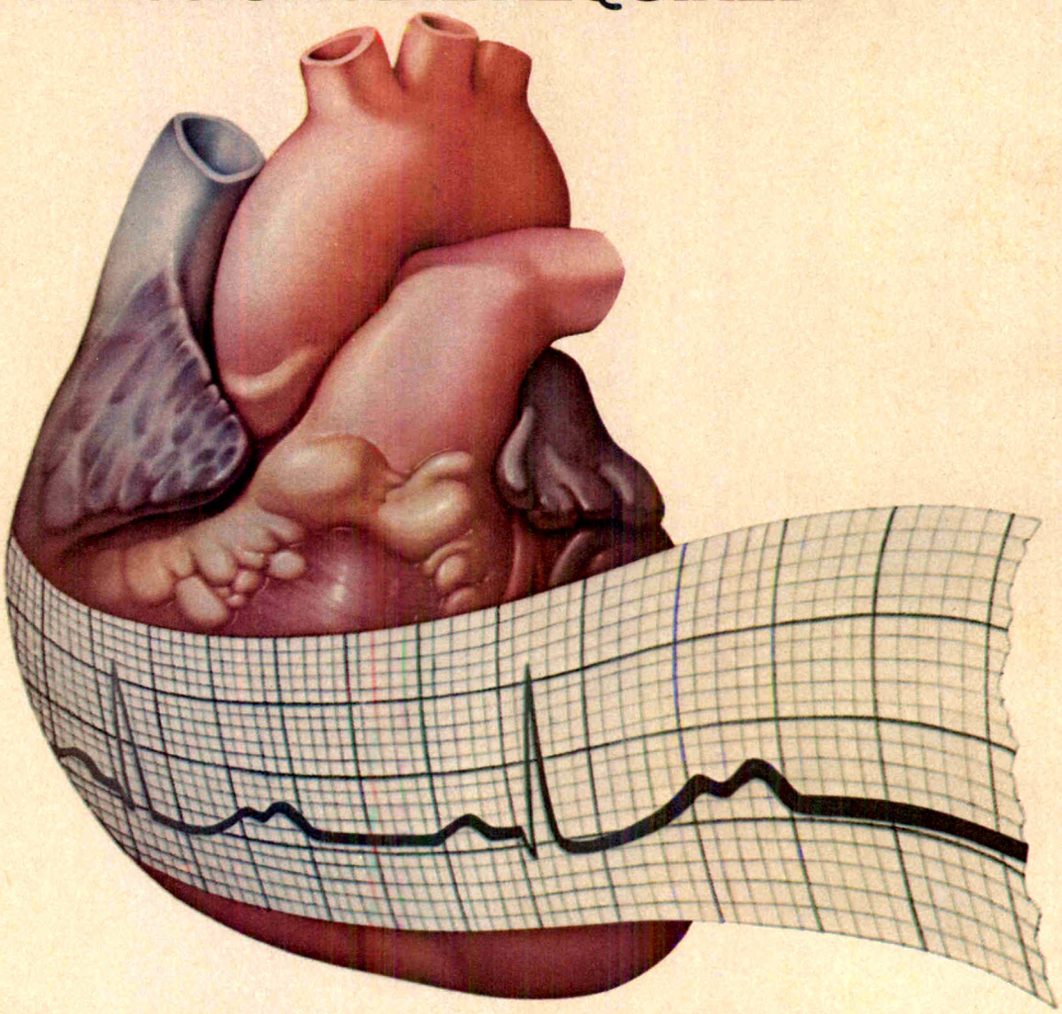
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Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

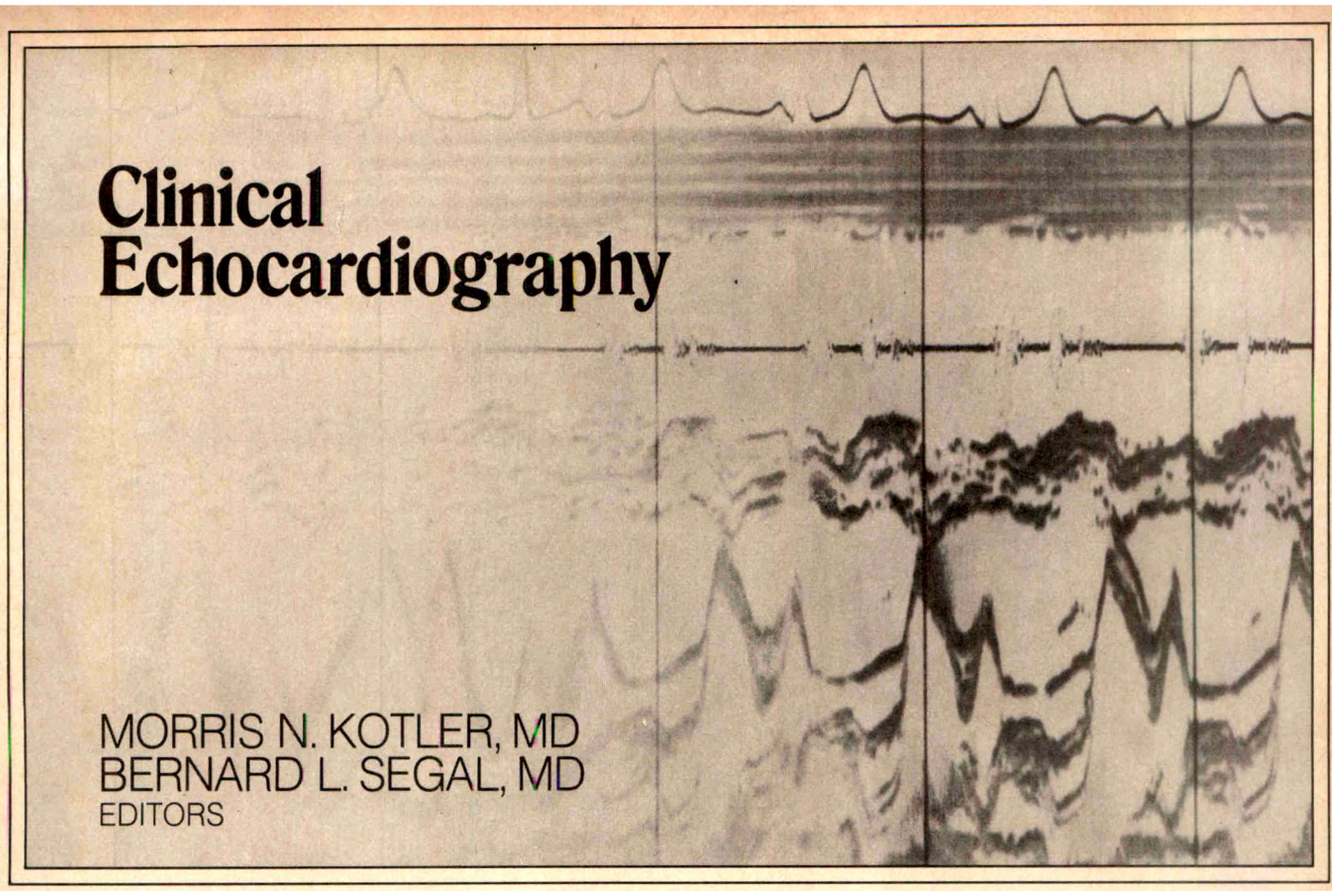
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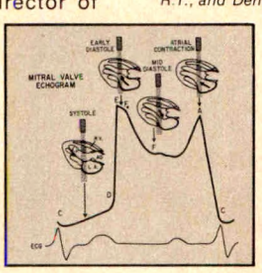
MORRIS N. KOTLER, MD
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EDITORS

A TIMELY NEW ADDITION TO THE CARDIOVASCULAR CLINICS SERIES.

VOLUME 9 NUMBER 2 — ALBERT N. BREST, MD, EDITOR-IN-CHIEF

Edited By **Morris Kotler, MD,** Associate Professor of Medicine, Director, Noninvasive Laboratories, William Likoff Cardiovascular Institute, Hahnemann Medical College and Hospital and **Bernard L. Segal, MD,** Professor of Medicine, Director of Services, William Likoff Cardiovascular Institute, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania.
373 pp/219 illus. (1978) $35.00

This text offers a sound and updated approach to the increasingly important noninvasive technique of echocardiography. It provides detailed information on the training of physicians and technicians, as well as the correlation with electrocardiography and heart sounds and murmurs. Individual chapters delineate specific types of disease in which echocardiography is most useful, as well as its limitations.



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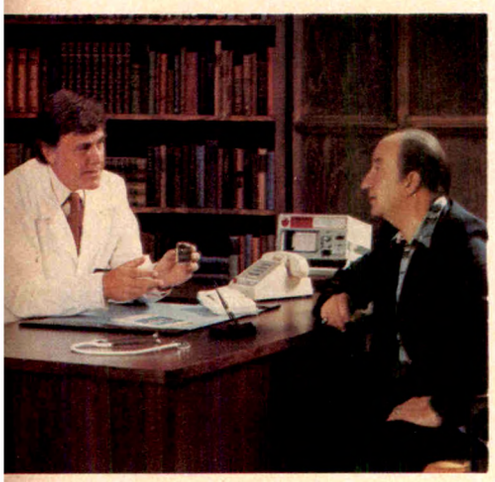
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A tungsten inert gas (TIG) welding technique is used to hermetically seal the InterLith in a 316L stainless steel enclosure that prevents moisture leakage. A specially designed polycrystalline ceramic feedthrough seal, utilizing a 99.99% pure platinum conductor, makes the electrical connection to the pulse generator. The high collar design of the feedthrough minimizes fluid leakage in the harsh environment of the human body.

The InterLith is one of the smallest, lightest pacemakers on the market. Its corners are gently beveled, much as the contours of the patient's own body, minimizing the risk of pressure necrosis. The unipolar model weighs only 75 grams (80 grams for the bipolar) and measures 6.0 cm by 4.6 cm by 1.5 cm, enabling a smaller incision and a more cosmetic pocket for greatest patient comfort. The InterLith's bipolar and unipolar configurations provide the physician with a choice for every pacing situation.

Confidence increases with superior performance.

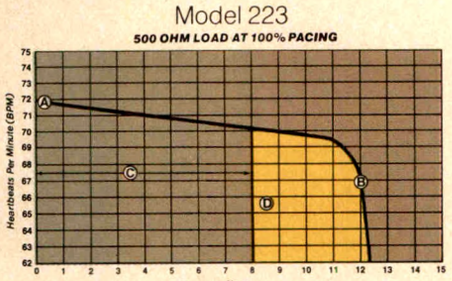
The InterLith's annual failure rate of less than .003 (at 90% confidence level) is largely attributable to the outstanding longevity of its lithium power cell, a battery without a single failure reported in 150,000 battery units manufactured. Combined with the proven reliability of c-mos circuitry, the InterLith provides superior performance at the lowest possible power consumption. This design represents sophisticated state-of-the-art technology in pacemaker electronics and gives the bipolar InterLith a theoretical longevity in excess of 11 years (12 years for the unipolar).*

Quality control insures confidence.

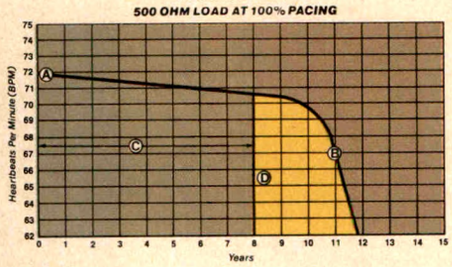
Every component utilized in the InterLith is selected and tested to meet the same standards as in the most exacting aerospace and military applications. Every step of the manufacturing process at Intermedics is subject to rigid quality assurance procedures in our complete environmental testing laboratory, because at Intermedics we believe only the highest quality products can merit your confidence. Some of the high reliability screening steps that our pacemakers receive in manufacturing are:

1. Twenty-four hour dynamic temperature cycling from −30° to +80° C.
2. Vibration testing at .1" displacement and 10 g's from 20 HZ to 2 KHZ.
3. Strip chart rate recording from room temperature to 60°C.
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Model 223



Model 224



A. Beginning of Life Rate (Determined 6 months following implantation of pulse generator). B. End of Service Rate (Loss of 7% from Beginning of Life Rate) C. Assured Service Life. D. Possible Extended Life (Depending on current drain and projected battery performance).*

**Computed assuming a 500 ohm load and 100% pacing. Assuming a more typical 750 ohm load and 50% pacing, longevity for the model 224 and model 223 would increase to 20 years and 22 years, respectively.*

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Intermedics Pulse Generators

INDICATIONS FOR USE Pacemakers may be used in any application where asynchronous or demand ventricular pacing is indicated. These include congenital or acquired complete heart block which may be continuous or intermittent in nature, various types of sinus node dysfunction, WPW syndrome, carotid sinus hypersensitivity, drug induced bradycardia, and various ventricular arrhythmias.

The above list is not intended to be complete. The indications for pacing are increasing as the devices become more sophisticated and as methods for patient management become more widely understood.

PRECAUTIONS Implanted cardiac pacemakers have a finite service life and a relatively wide variability in service life. Factors affecting service life include the initial capacity of the battery and the shelf storage time of the manufactured pulse generator. Once implanted the anticipated service life of the generator is modified by variations in electrode system resistances, stimulation rate, and the percentage of time during which the pacemaker is inhibited. The current drain on the battery when inhibited is less than one-third of that when pacing with a typical lead installation. Other factors contributing to wide variability in service life are random electronic component failures.

All sensing pulse generators are inherently susceptible to magnetic electrical and electromagnetic fields. While design features are incorporated to minimize this susceptibility, an extraneous signal of sufficient strength and with characteristics which mimic normal cardiac activity can influence their operation. Additionally, certain environmental sources can couple sufficient energy into a cardiac pacemaker system to damage the pulse generator. Specifically, the implanting physician and the patient should be warned about the following:

(1) Electrocautery–Surgical use of electrocautery may cause temporary inhibition of the pulse generator. Additionally, pulse generator damage is possible if sufficient energy is coupled into it. Use of electrocautery within 4-5 centimeters of the implanted pacemaker can cause a direct coupling of RF energy through the lead and electrode to the cardiac muscle, producing burns or possible ventricular fibrillation.

Continuous monitoring of blood pressure and pulse should be instituted in all procedures where the use of electrocautery is contemplated. The ground plate of the electrocautery system should be placed in a manner to minimize current flow through the pacing system. A specific example is a TUR; during this procedure, the ground plate should be placed low on the buttocks or strapped to the thigh.

(2) Diathermy–A pacemaker patient should not receive this form of therapy. Very intense fields of microwave energy are involved and reactions of all sensing pulse generators are unpredictable. Total or virtually complete inhibition of the pacing circuitry is possible; however, no damage will result to the circuitry during the exposure.

(3) Microwave Ovens-Ovens, both in the home and in commercial use, in good condition and used as intended, or any microwave appliance which does not exceed federal guidelines of 0.5 milliwatts/cm² leakage at a point 2.5cm. from the appliance will not affect Intermedics pulse generators. However, appliances have been discovered which emit radiation in excess of 200 times these guidelines. The possibility of interference from such defective appliances does exist. The pulse generator will not be damaged by such exposure.

(4) Defibrillation–All implanted unipolar pulse generators regardless of manufacturer, can be damaged by cardiac defibrillation. Additionally, the presence of an implanted pacemaker system can increase the amount of cardiac muscle damage which results from defibrillation.

(5) Home Electrical and Gasoline Powered Appliances–Certain electrical and gasoline powered appliances can cause inhibition of an implanted cardiac pacemaker system. Pacemaker patients should be warned about the possibilities of pulse generator inhibition from some electric razors, most notably the rotary types, hand-held electric drills, power saws, and other appliances containing brush motors.

CONTRAINDICATIONS AND SIDE EFFECTS There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. The patient diagnosis and prognosis may indicate the type of pacemaker therapy used by the physician.

Body rejection phenomenon, local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism and cardiac tamponade have been reported from the use of implanted cardiac pacemakers.

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WARNING

Spironolactone, an ingredient of Aldactazide, has been shown to be a tumorigen in chronic toxicity studies in rats (see *Warnings*). Aldactazide should be used only in those conditions described under *Indications*. Unnecessary use of this drug should be avoided.

Fixed-dose combination drugs are not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Indications: Cirrhosis of the liver accompanied by edema and/or ascites. Essential hypertension, edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate.

Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, hyperkalemia or acute or severe hepatic failure. Allergy to thiazide diuretics or to other sulfonamide-derived drugs.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactazide. Do not administer concurrently with other potassium-sparing diuretics. Sulfonamide derivatives including thiazides have been reported to exacerbate or activate systemic lupus erythematosus.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75 and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hypokalemia may develop as a result of profound diuresis, particularly when Aldactazide is used concomitantly with loop diuretics, glucocorticoids or ACTH. Transient elevation of BUN may occur. Dilutional hyponatremia or rarely low-salt syndrome may develop. Gynecomastia may develop and in rare instances some breast enlargement may persist.

Thiazides may alter the metabolism of uric acid and carbohydrates with possible hyperuricemia, gout and decreased glucose tolerance. Vascular responsiveness to norepinephrine is reduced. Thiazides may also increase the responsiveness to tubocurarine. Thiazides may decrease serum PBI levels and prolonged therapy may induce hypercalcemia and hypophosphatemia.

Spironolactone may and hydrochlorothiazide does cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. Breast feeding should be discontinued when Aldactazide is being used.

Adverse Reactions:

Associated with spironolactone: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established.

Associated with thiazides: Gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhea, abdominal cramps), purpura, thrombocytopenia, leukopenia, agranulocytosis, dermatologic symptoms (cutaneous eruptions, pruritus, erythema multiforme), paresthesia, acute pancreatitis, jaundice, dizziness, vertigo, headache, xanthopsia, photosensitivity, necrotizing angiitis, aplastic anemia, orthostatic hypotension, muscle spasm, weakness and restlessness.

Adverse reactions are usually reversible upon discontinuation of Aldactazide.

Dosage and Administration

Edema in adults: The usual maintenance dose is one tablet four times daily but may range from one to eight tablets daily depending on the response to the initial titration.

Edema in children: The usual daily maintenance dose should be that which provides 0.75 to 1.5 mg. of spironolactone per pound of body weight (1.65 to 3.3 mg./kg.).

Essential hypertension: Usually two to four tablets daily depending on results of the titration of the individual ingredients.

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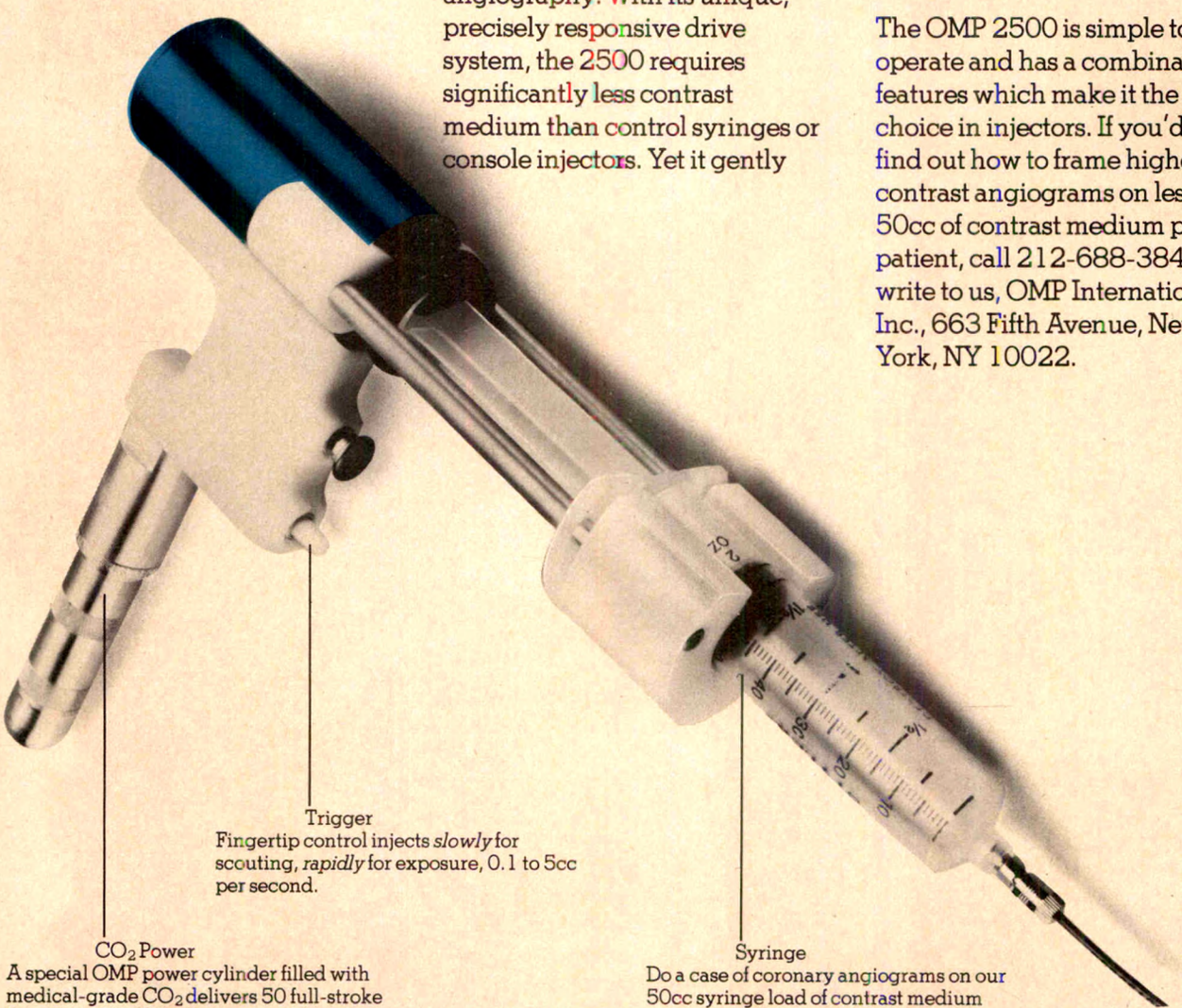
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Hypertensive Pulmonary Vascular Disease in *d*-Transposition of the Great Arteries

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In subjects with classic complete transposition (*d*-transposition) of the great arteries, the pulmonary arterial plexiform lesion, characteristic of chronic high levels of pulmonary arterial pressure, was observed in those with an intact ventricular septum as well as in those with a ventricular septal defect. The lesion was not observed before age 12 months. Among 16 patients aged 12 to 30 months, the plexiform lesion was observed in 6 of 12 patients (50 percent) with an intact ventricular septum and a closed ductus arteriosus and in 1 of 4 patients with an associated ventricular septal defect. The basis of the plexiform lesion, which is considered a sign of chronic severe pulmonary hypertension, occurring in subjects with an intact ventricular septum and a closed ductus arteriosus is not explained. The phenomenon observed in this study confirms the earlier observations of others.

In classic complete transposition (*d*-transposition) of the great arteries, the tendency for the pulmonary arterial vasculature to show hypertensive changes was first identified by Ferguson et al.[1] in 1960. They demonstrated abnormal degrees of medial thickening even when the ventricular septum was intact. Later, in 1966, Ferencz[2] confirmed these observations and, in addition, showed that plexiform lesions could occur under the same conditions. Since then, others[3–7] have made similar pathologic observations. Functional studies[8,9] have shown that pulmonary hypertension is commonly present in *d*-transposition with or without a ventricular septal defect. Its underlying basis is a high level of pulmonary vascular resistance.

The plexiform lesion is generally considered a sign that severe degrees of pulmonary hypertension had been present and that the pulmonary hypertension is usually irreversible. In conditions such as isolated ventricular septal defect, this lesion is not usually observed before the age of about 3 years; however, in *d*-transposition it has been seen at earlier ages even when the ventricular septum is intact. Reports that hypertensive pulmonary vascular disease occurs in *d*-transposition with an intact ventricular septum and at early ages stimulated us to study the pulmonary vascular bed in this condition.

Materials and Methods

The material for this study is in the collection of cases with *d*-transposition in the Cardiovascular Registry of United Hospitals-Miller Division. The study group comprised the 35 cases that fulfilled the following criteria: (1) age of patient between 1 and 30 months, (2) absence of pulmonary stenosis, (3) closed ductus arteriosus, (4) no operative intervention except creation of an atrial septal defect, and (5) presence of both lungs in the specimen.

The 35 cases were separated into two major groups, as follows: those with an intact ventricular septum (Group I, 24 cases) and those with a ventricular septal defect (Group II, 11 cases). Each group was further separated into two subgroups according to the patients' ages; patients aged 1 to 11 months were classified into Subgroup a, and those aged 12 to 30 months into Subgroup b.

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TABLE I

Hypertensive Pulmonary Vascular Disease in 35 Cases of *d*-Transposition of Great Arteries

Group and Subgroup	Patients (no.)	Grade of Hypertensive Pulmonary Vascular Disease				
		0	1	2	3	4
Group I: *d*-Transposition With Intact Ventricular Septum						
Ia	12 (50)	0 (0)	9 (75)	3 (25)	0 (0)	0 (0)
Ib	12 (50)	1 (8)	4 (33)	0 (0)	1 (8)	6 (50)
Total	24 (100)	1 (4)	13 (54)	3 (13)	1 (4)	6 (25)
Group II: *d*-Transposition With Ventricular Septal Defect						
IIa	7 (64)	0 (0)	2 (29)	5 (71)	0 (0)	0 (0)
IIb	4 (36)	1 (25)	2 (50)	0 (0)	0 (0)	1 (25)
Total	11 (100)	1 (9)	4 (36)	5 (45)	0 (0)	1 (9)

Figures in parentheses indicate percent of patients. Subgroup a = patients aged 1 to 11 months of age; subgroup b = patients aged 12 to 30 months.

Grading of pulmonary vascular disease: In every case, at least one section was obtained from each pulmonary lobe. Duplicate sections were stained with hematoxylin-eosin and by the elastic-van Gieson method. In each case, the nature of the pulmonary arterial vessels was determined using the histologic grading system proposed by Heath and Edwards[10]: grade 0, normal pulmonary vessels; grade 1, medial hypertrophy; grade 2, intimal proliferation; grade 3, intimal fibrosis, and grade 4, plexiform lesions. No grade 5 dilatation lesions or grade 6 arteritis was observed.

Results

All patients had either a congenital narrowly patent foramen ovale or an atrial septal defect created surgically with the Blalock-Hanlon or Rashkind procedure.

Of the 24 subjects in Group I (those with an intact ventricular septum) 12 (9 male, 3 female) were in Subgroup Ia (age 1 to 6 months; mean 3 months) at the time of death, and 12 (7 male, 5 female) were in Subgroup Ib (age 12 to 30 months; mean 19 months) at death.

Of the 11 subjects in Group II (those with a ventricular septal defect) 7 (3 male, 4 female) were in Subgroup IIa (age 2 to 8 months; mean 5 months), and 4 (3 male, 1 female) were in Subgroup IIb (age 12 to 30 months; mean 21 months) at the time of death. Table I lists the grade of pulmonary vascular changes in the identified subgroups. There were no instances of grade 5 or grade 6 lesions.

In Subgroup Ia (intact ventricular septum, less than 12 months of age), none showed lesions greater than grade 2, whereas in Subgroup Ib (age 12 to 30 months), 6 of 12 (50 percent) showed plexiform lesions, allowing a designation of grade 4 (Fig. 1).

In Subgroup IIa (ventricular septal defect, less than 12 months of age), none showed lesions greater than grade 2. In contrast, in Subgroup IIb (ventricular septal defect, age 12 to 30 months), grade 4 lesions were present in one of four subjects (25 percent) (Fig. 2).

Comment

Since 1960, investigators[1–9] have reported the tendency of patients with *d*-transposition of the great arteries to have hypertensive pulmonary vascular disease at an earlier age than is common in patients with other forms of congenital cardiac disease. Although severe

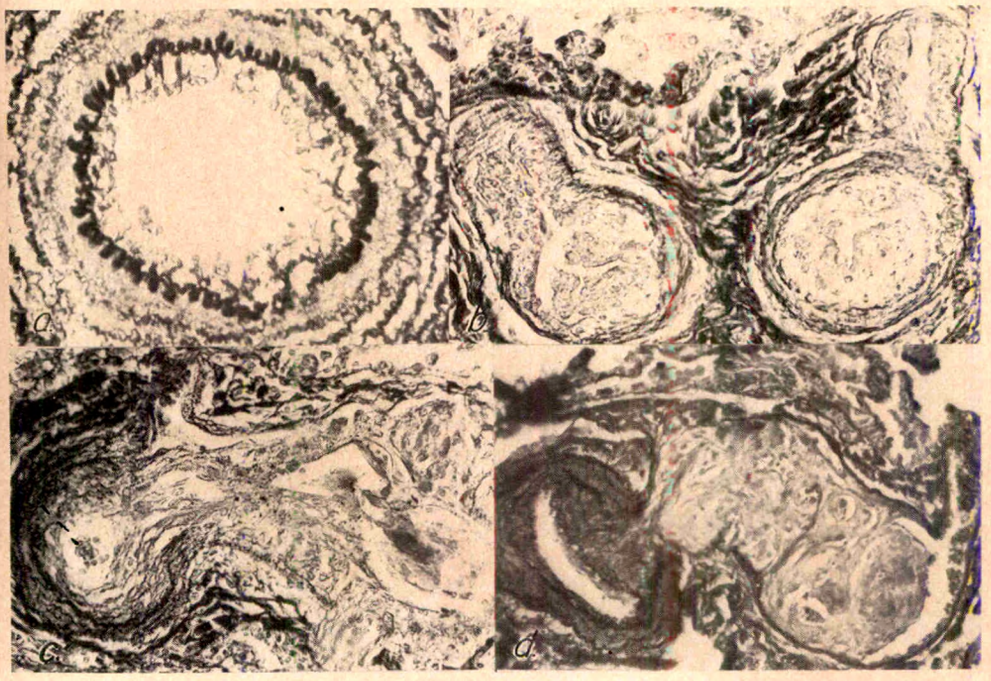


FIGURE 1. Photomicrographs of muscular pulmonary arteries in *d*-transposition with intact ventricular septum (Group I). ***a,*** grade 1 pulmonary vascular hypertension (5 month old boy); ***b,*** grade 2 (1 month old girl); ***c,*** grade 4 (12 month old girl); ***d,*** grade 4 (30 month old boy). (Elastic-van Gieson stain ×200 [***a***], ×180 [***b*** and ***c***] and ×120 [***d***], all reduced by 15 percent.)

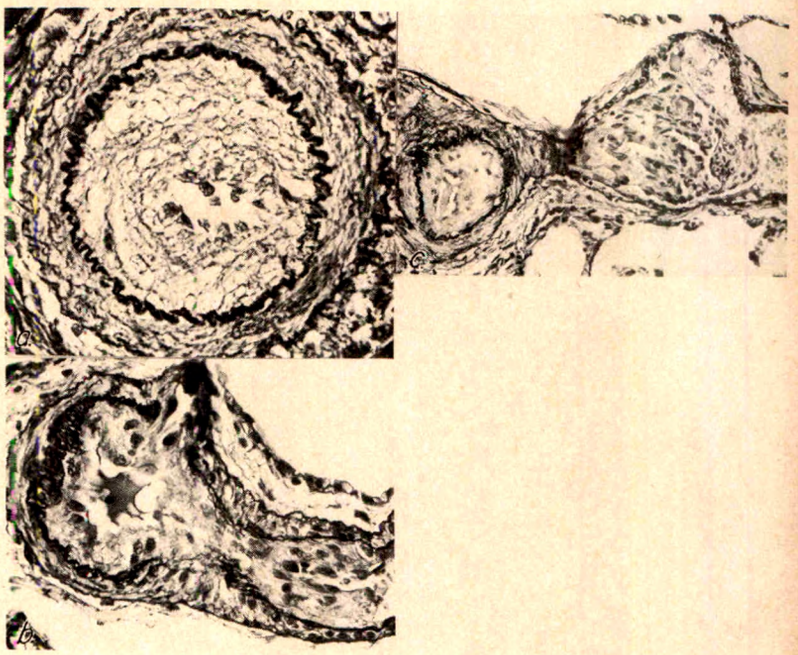


FIGURE 2. Photomicrographs of muscular pulmonary arteries in patients with *d*-transposition with ventricular septal defect (Group II). ***a,*** grade 2 pulmonary vascular hypertension (8 month old boy); ***b,*** early grade 4 (12 month old boy); ***c,*** grade 4 (12 month old boy). (Elastic van Gieson stain ×360 [***a*** and ***b***] and ×180 [***c***], all reduced by 11 percent.)

forms of pulmonary vascular disease rarely develop before age 3 years in most other types of congenital cardiac disease, in *d*-transposition they have been reported to occur during the first year of life[5,7] and frequently during the second year.[4,5,8] Our studies confirm these observations. Many investigators have emphasized that palliative surgical procedures to protect the pulmonary vasculature should be performed as early as possible,[1,4] preferably during the first year of life[7] or even during the first 6 months.[5]

Investigators have proposed that in *d*-transposition the severe pulmonary vascular disease is secondary to the presence of either a large ventricular septal defect[2,3,5,9] or a patent ductus arteriosus.[5] However, this study and those of others[4,7] have shown that severe hypertensive pulmonary vascular disease may develop in patients with *d*-transposition in whom shunting occurs only at the atrial level. Clarkson et al.[7] reported that 15 to 20 percent of their patients aged 3 to 11 months had advanced (grade 3 or greater) pulmonary vascular disease. Ferencz[2] observed plexiform lesions at age 6 weeks and at age 3 months in subjects with an intact ventricular septum.

In our series of patients with *d*-transposition, no patient less than 1 year of age had greater than grade 2 pulmonary vascular lesions; among these, most patients with an intact ventricular septum had grade 1 lesions, whereas most with a concomitant ventricular septal defect had grade 2 lesions. However, most of our patients in this age group were less than 6 months old. The small number of our patients aged 6 to 11 months may well explain this discrepancy with the work of others,[2,7] who found grade 3 or 4 lesions present in the first year of life.

In our study, patients aged 12 to 30 months frequently had grade 4 (plexiform) lesions in the pulmonary arteries. Fifty percent of those with an intact ventricular septum had grade 4 lesions, whereas one of the four patients (25 percent) with a ventricular septal defect had grade 4 (plexiform) lesions. The difference in incidence of grade 4 lesions between our two primary groups may be a reflection of a small number of cases and probably is not significant.

Causes of pulmonary vascular disease in presence of intact ventricular septum: Because severe hypertensive pulmonary vascular disease develops in cases of *d*-transposition with an intact ventricular septum and a closed ductus arteriosus, one must consider causes of pulmonary hypertension other than a communication between the ventricles or great arteries. Three possible causes have been considered: (1) a shunt at the atrial septal level, (2) a shunt through the bronchial arterial circulation, and (3) inherent structural defects in the muscular pulmonary arteries.

Because isolated shunts at the atrial septal level rarely lead to significant hypertensive pulmonary vascular disease until the third decade of life,[1] it is doubtful that such a shunt alone would result in plexiform lesions in patients with *d*-transposition. Although in *d*-transposition the bronchial arteries are usually dilated and may supply significant flow of blood to the lungs,[2] this process alone probably does not contribute significantly to the development of pulmonary hypertension. In support of this negative view is the fact that irreversible pulmonary hypertension rarely (if ever) develops in patients with tetralogy of Fallot with severe pulmonary stenosis and extensive bronchial arterial collateral vessels.[11]

Yamaki and Tezuka[6] recently suggested that patients with *d*-transposition may have structural defects of the

muscular pulmonary arteries that predispose to the development of hypertensive pulmonary vascular disease. They reported that, although the pulmonary vascular change of *d*-transposition and of isolated ventricular septal defects were the same until age 5 months, after this age the grade of pulmonary vascular disease in *d*-transposition was much greater than that in isolated ventricular septal defect. They also noted that the amount of medial hypertrophy of pulmonary arteries was less in patients with *d*-transposition than in patients of all ages with an isolated ventricular septal defect. From this, they hypothesized that the inherent lack of medial muscular support in pulmonary arteries may allow the development of severe hypertensive pulmonary vascular disease at an early age in response to pulmonary hypertension, when present.

Implication: One cannot disprove the concept that the pulmonary arterial vessels are peculiarly different in *d*-transposition from those in other conditions. Nevertheless, the structural changes must be viewed as a result rather than a cause of pulmonary hypertension. The basis for the occurrence of pulmonary hypertension in *d*-transposition with intact ventricular septum remains an unexplained fundamental question.

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Comparative Hemodynamic Effects of Intravenous Nitroprusside And Oral Prazosin in Refractory Heart Failure

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Beneficial effects of vasodilator therapy in heart failure have been amply described. Afterload reduction with intravenous nitroprusside improves hemodynamic values in patients with left ventricular dysfunction. The oral vasodilator prazosin was given to 10 patients with refractory heart failure, and its hemodynamic effects were compared with those of intravenous nitroprusside in the same patients. With prazosin, heart rate remained unchanged, mean arterial pressure decreased 13 percent ($P < 0.01$), left ventricular filling and mean pulmonary arterial pressures decreased 31 and 24 percent, respectively (both $P < 0.01$), and cardiac index and left ventricular stroke work increased by 31 and 30 percent, respectively (both $P < 0.01$). Resistance levels in the systemic and pulmonary vascular beds declined by 29 and 27 percent, respectively (both $P < 0.01$). The hemodynamic changes appeared 1 hour after administration of a single dose of oral prazosin and persisted for 6 hours.

Intravenous infusion of nitroprusside resulted in similar changes in heart rate and arterial pressure but greater reduction in left ventricular filling and mean pulmonary arterial pressures ($P < 0.05$). Left ventricular stroke work index increased more with nitroprusside ($P < 0.01$); however, changes in cardiac index and systemic and pulmonary vascular resistance levels were identical. Further, systolic pressure-heart rate product (index of myocardial oxygen demand) decreased significantly with oral prazosin as well as nitroprusside. These results suggest that prazosin has salutary effects on cardiovascular hemodynamics in heart failure, probably because of its vasodilator properties. These effects are qualitatively similar to those observed with intravenous infusion of nitroprusside. However, quantitatively, intravenous nitroprusside is slightly more potent.

A decrease in left ventricular afterload in patients with heart failure has been shown to improve left ventricular function by increasing stroke volume and decreasing left ventricular filling pressure.[1–3] This beneficial effect occurs in heart failure associated with a variety of pathologic states, including coronary heart disease,[1,2] mitral and aortic regurgitation[4,5] and hypertensive heart disease.[6] Reduction of preload, on the other hand, decreases left ventricular filling pressure but does not consistently result in improved stroke volume.[7,8] In some patients a decrease in preload such as that resulting with potent diuretic or venodilator agents like nitrates, while reducing congestion, may result in decreased cardiac output.[9] Thus it is often necessary to evaluate precisely a given agent's variable effects on preload and afterload according to the individual patient's hemodynamic responses.

Intravenously administered nitroprusside produces a rapid change in cardiac output and reduction in left ventricular filling pressure in certain patients with heart failure because of afterload reduction. Its action is of short duration and, once the drug is withdrawn, the salutary effects are reversed. Because nitroprusside must be given parenterally,

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its usefulness is limited to in-hospital patients. Thus, to broaden conventional long-term management of heart failure, currently limited to administration of digitalis and diuretic agents, other nonparenteral measures to increase stroke volume and decrease pulmonary congestion are clinically desirable. Hydralazine, an oral agent with a predominant arteriolar dilator action,[10–12] has shown promise in initial studies in patients with heart failure.[13,14] However, in early studies it did not consistently reduce left ventricular filling pressure,[13] probably because it lacks venodilator properties.

Prazosin, a quinazoline derivative used orally in the therapy of hypertension, has both arterial resistance and venous capacitance vessel dilator effects.[15] Therefore, this study was designed to evaluate the effects of prazosin-induced reduction of afterload as well as preload in patients with intractable heart failure. In addition, the effects of prazosin were compared with those of nitroprusside administered intravenously in the same patients.

Methods

Patient selection: The study group comprised 10 men (aged 37 to 61 years) with symptoms and signs of clinical heart failure despite treatment with digitalis, diuretic agents and salt restriction. The duration of heart failure ranged from 3 to 7 years before the study. All 10 patients had cardiomegaly. A ventricular gallop was evident in six patients and bibasilar pulmonary rales in seven. All subjects were in New York Heart Association[16] functional class[16] III or IV at the time of study. All patients had heart failure secondary to coronary heart disease as documented in the history, electrocardiograms and previous coronary angiograms. None had angina at the time of study. Each patient had areas of abnormal motion noted during left ventriculography. All patients had sinus rhythm, although three had evidence of occasional atrial or ventricular ectopy.

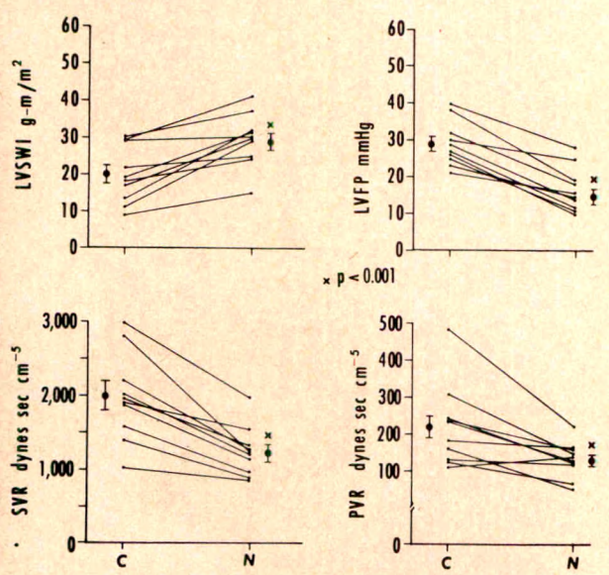


FIGURE 1. Hemodynamic response to nitroprusside (N) infusion in 10 patients with refractory heart failure. Left ventricular filling pressure (LVFP) decreased and left ventricular stroke index (LVSWI) increased in association with a decrease in systemic (SVR) and pulmonary vascular resistance (PVR) levels. C = control.

Hemodynamic studies: The studies were performed in a special study room of the cardiac care unit so that hemodynamic variables could be monitored and recorded throughout the study. Use of nitrates was discontinued at least 2 days before the study. Administration of all other medications, including digitalis and diuretic and antiarrhythmic agents, was continued. Patients were kept at bed rest for at least 8 hours before the study to achieve a steady state. After the procedure was explained and informed consent obtained, a triple lumen, flow-directed catheter was inserted into the pulmonary artery. A Teflon® catheter was introduced percutaneously into the radial artery to measure systemic blood pressure. Systemic and pulmonary arterial pressures and pulmonary capillary wedge pressure were recorded on an Electronics for Medicine VR-6 recorder with P231A Statham strain gauge transducers. Mean pressures were obtained with use of electronic filtration. Systolic and diastolic pressures were averaged from at least 10 beats recorded during two respiratory cycles. Occluded pulmonary arterial pressure recorded during balloon inflation agreed closely with pulmonary arterial diastolic pressure in each patient. Thus, either pressure measurement was used as an index of left ventricular filling pressure. All pressure measurements were referenced to the mid chest. Heart rate was averaged from recordings of a standard electrocardiographic lead. Cardiac output was measured in triplicate with the thermodilution technique[17] using a thermodilution computer (Edwards Laboratory, Santa Ana, California), and the data were reported as the average of these three determinations.

The following calculations were made: CI = CO/BSA (liters/min per m^2); SV = CO/HR (ml/beat); LVSWI = SVI × ($\overline{Ao}$ − LVFP) × 0.0136 (g −m/m^2); SVR = $\overline{Ao}$ × 80/CO dynes sec cm^{-5}; and PVR = $\overline{PA}$ − LVFP) × 80/CO dynes sec cm^{-5}, where CI = cardiac index, CO = cardiac output, BSA = body surface area, SV = stroke volume, HR = heart rate, LVSWI = left ventricular stroke work index, SVI = stroke volume index, $\overline{Ao}$ = mean arterial pressure, LVFP = left ventricular filling pressure, SVR = systemic vascular resistance, $\overline{PA}$ = mean pulmonary arterial pressure and PVR = pulmonary vascular resistance.

All values are expressed as mean ± standard error of the mean. The paired Student's *t* test was used to determine the statistical significance of comparisons. A probability (*P*) value of less than 0.05 was considered significant.

Study protocol: In five patients nitroprusside was administered intravenously before prazosin, and in the other five prazosin was given first. Nitroprusside was infused starting at 10 μg/min; the dose was increased by 10 μg/min every 10 minutes until there was a decrease in left ventricular filling pressure, an increase in cardiac output or a change in systolic arterial pressure (20 mm Hg reduction from control value or 100 mm Hg, whichever appeared first). After hemodynamic measurements, including determinations of heart rate, systemic and pulmonary arterial pressures and cardiac output, were made at each dose level, nitroprusside infusion was discontinued and the hemodynamic values allowed to return to control level. Thereafter, 4 mg of prazosin was administered orally and hemodynamic data were recorded every hour for 6 hours.

In the other five patients the effects of prazosin were measured first and then the hemodynamic values were allowed to return to the preprazosin level, which took an average of 18 hours. Nitroprusside was administered thereafter according to the protocol described.

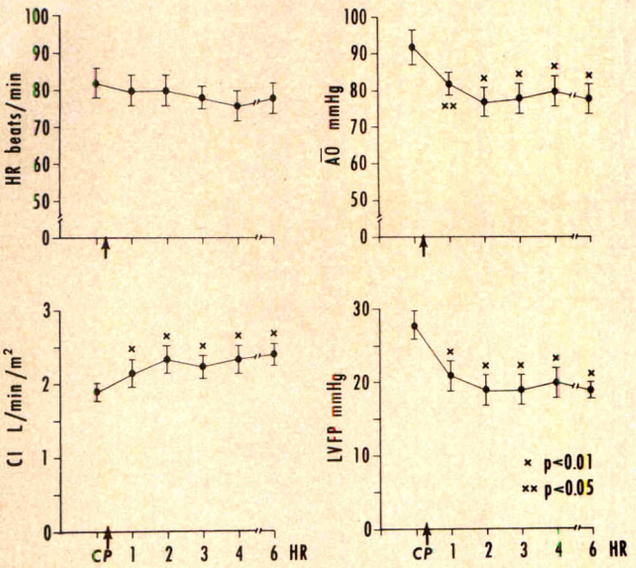


FIGURE 2. Hemodynamic response to oral prazosin in 10 patients with refractory heart failure. Hemodynamic alterations were apparent at 1 hour and persisted for 6 hours after prazosin (P) administration (**arrows** point to the time of administration). $\overline{AO}$ = mean systemic arterial pressure; C = control; CI = cardiac index; HR = heart rate; L = liters; LVFP = left ventricular filling pressure; p = probability;

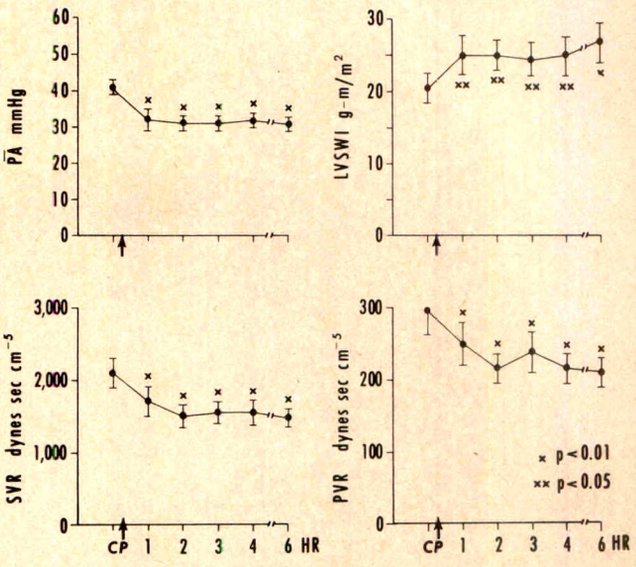


FIGURE 3. Hemodynamic responses to oral prazosin. The decrease in mean pulmonary arterial pressure (PA) and systemic (SVR) and pulmonary (PVR) vascular resistances levels and the increase in left ventricular stroke work index (LVSWI) appeared at 1 hour (HR) and persisted for 6 hours after administration of prazosin (P). C = control; p = probability.

Results

Nitroprusside: Infusion of nitroprusside (in a dose ranging from 20 to 200 μg/min) resulted in no change in heart rate (80 ± 5 versus 85 ± 5) (difference not significant). Mean arterial pressure decreased from 88 ± 4 to 78 ± 4 mm Hg (P <0.01). Cardiac index increased from 2.02 ± 0.18 to 2.77 ± 0.16 liters/min per m^2 (P <0.001) and left ventricular filling pressure decreased from 29 ± 2 to 14 ± 2 mm Hg (P <0.001). Mean pulmonary arterial pressure also decreased from 40 ± 2 to 25 ± 2 mm Hg (P <0.001). Left ventricular stroke work index increased from 19.87 ± 2.45 to 29.28 ± 2.24 g −m/m^2 (P <0.001), in association with a significant decrease in systemic from 1,994 ± 199 to 1,237 ± 106 dynes sec cm^{-5} (P <0.001) and pulmonary from 221 ± 36 to 131 ± 15 dynes sec cm^{-5} (P <0.001) vascular resistance levels (Fig. 1). Heart rate-systolic arterial pressure product decreased significantly with infusion of nitroprusside from 11,331 ± 785 to 9,874 ± 827 beats/min per mm Hg (P <0.01). These hemodynamic effects, seen in each patient shortly after nitroprusside infusion, abated as soon as infusion was discontinued.

Oral prazosin: Significant alterations in hemodynamics were observed 1 hour after administration and these changes persisted up to 6 hours. A tendency toward return to preprazosin levels was observed thereafter. Hemodynamic values returned to control level in all patients within 24 hours of administration of a single dose. Heart rate remained unchanged throughout the study period (Fig. 2). In every patient mean arterial pressure was reduced throughout the study period, decreasing to a mean of 78 ± 4 from 92 ± 5 mm Hg (P < 0.01).

Cardiac index increased from the control value of 1.92 ± 0.13 to 2.39 ± 0.16 liters/min per m^2 at 6 hours (P <0.01). Although cardiac index improved in every patient, the maximal increase was not observed at 1 hour in every patient. However, at the end of the 6 hour period, cardiac index was 11 to 63 percent higher (mean 31 ± 6 percent) than in the control period. Stroke volume increased from 45.5 ± 4.6 to 59.3 ± 5.4 ml/beat (P < 0.01).

Left ventricular filling pressure was decreased at 1 hour (Fig. 2). At 6 hours, a 52 percent decrease was apparent (19 ± 1 versus 28 ± 2 mm Hg) (P <0.01). The reduction in filling pressure occurred in all 10 patients and ranged from 4 to 51 percent of preprazosin levels.

Mean pulmonary arterial pressure decreased from 41 ± 2 to 31 ± 2 mm Hg (P <0.01). Left ventricular stroke work index increased from 20.61 ± 2.1 to 26.86 ± 2.26 g −m/m^2 (P <0.01). Stroke work index increased significantly at 1 hour and was higher throughout the study period (Fig. 3).

Resistance levels in the arterial and pulmonary beds declined with a single dose of prazosin. This decline was observed throughout the study period (Fig. 3). Systemic vascular resistance at 6 hours was 1,472 ± 116, compared with 2,118 ± 208 dynes sec cm^{-5} in the control period (P <0.01) and pulmonary vascular resistance decreased to 209 ± 19 from 295 ± 27 dynes sec cm^{-5} (P <0.01). The reduction in systemic vascular resistance was seen in every patient and pulmonary vascular resistance was reduced in all but one.

Heart rate-systolic arterial pressure product declined by 12 percent from a control value of 10,687 ± 776 to 9,447 ± 607 beats/min per mm Hg (P < 0.02) at the end of the study period.

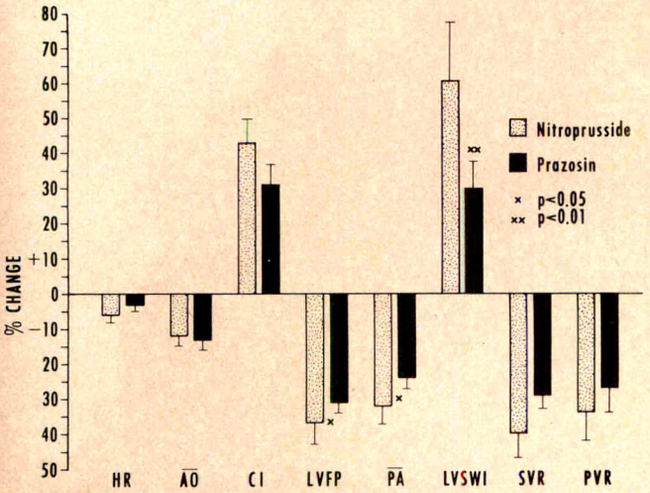


FIGURE 4. Percent change in cardiovascular hemodynamics at peak effect of intravenous nitroprusside and oral prazosin in the 10 patients. A decrease in systemic arterial (AO), left ventricular filling (LVFP) and pulmonary arterial pressures (PA) and systemic (SVR) and pulmonary (PVR) vascular resistance levels occurred in association with an increase in cardiac index (CI) and left ventricular stroke work index (LVSWI). HR = heart rate; p = probability.

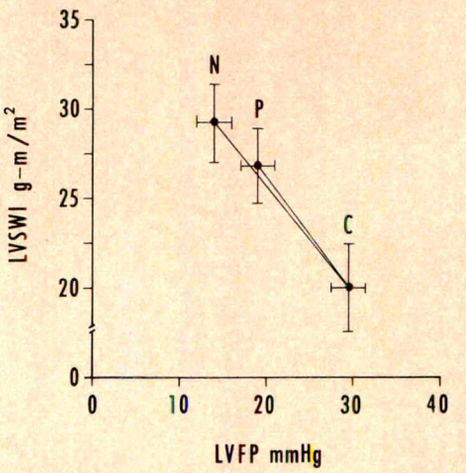


FIGURE 5. Effect of intravenous nitroprusside (N) and oral prazosin (P) on the relation between left ventricular filling pressure (LVFP) and stroke work index (LVSWI). Both agents moved this relation upward and to the left. Nitroprusside appears to be slightly more potent. C = control.

Nitroprusside versus prazosin: Comparative hemodynamic effects in the 10 patients are shown in Figure 4. Heart rate did not change significantly with either agent. The reduction in mean arterial pressure with nitroprusside was 12 ± 2.5 percent and with prazosin 13 ± 3 percent (difference not significant). Cardiac index increased by 42 ± 9 percent with nitroprusside and 31 ± 6 percent with prazosin (differences not significant). The decrease in left ventricular filling pressure was greater with nitroprusside (37 ± 6 percent) than with prazosin (31 ± 4 percent) ($P < 0.05$).

The reduction in mean pulmonary arterial pressure was greater with nitroprusside than with prazosin (32 ± 5 versus 24 ± 3 percent) ($P < 0.05$). Left ventricular stroke work index increased by 61 ± 17 percent with nitroprusside infusion, but by only 30 ± 8 percent with prazosin ($P < 0.01$). The decrease in systemic vascular resistance appeared to be greater with nitroprusside (40 ± 7 versus 29 ± 4 percent) and a similar difference was apparent in pulmonary vascular resistance (34 ± 8 versus 27 ± 7 percent), but these differences were not statistically significant.

Complications: No untoward side effects were observed with nitroprusside infusion. With prazosin, no patient manifested hypotension, tachycardia or evidence of myocardial ischemia. Two patients initially had nausea that gradually disappeared. One subject reported constant mild headache while his aortic pressure was maintained and cardiac output increased. Headache abated in 3 hours spontaneously. Occasional atrial and ventricular ectopy developed in one patient but no therapy was required. Atrial premature complexes became more frequent in another patient requiring no additional treatment.

Clinical evaluation: While the hemodynamic effects of prazosin were apparent, all 10 patients reported noticeable alleviation of symptoms of low cardiac output such as fatigue and weakness. Symptoms of pulmonary congestion, that is, orthopnea and dyspnea, decreased markedly in five patients and to a lesser degree in three others during the study period. Examination revealed that the limbs were warmer than in the preprazosin state. In the six patients with a ventricular gallop before therapy, it disappeared in four and became softer in intensity in two. Basilar rales on pulmonary examination also decreased in all seven patients with rales before treatment.

Overall, all patients accepted prazosin treatment without any untoward effect. Hypotension was not noted in any patient. Seven patients were discharged on a regimen of oral prazosin, 4 mg every 6 hours, in addition to digitalis, diuretic and antiarrhythmic agents and salt restriction.

Discussion

Effects of nitroprusside: Administration of nitroprusside in patients with left ventricular dysfunction has been amply shown to be beneficial[1–3] and has become a standard practice. The beneficial effects of nitroprusside in heart failure are hypothesized to be due to its effect on the resistance (afterload) as well as capacitance (preload) vessels.[1–3,18] However, these salutary effects are of short duration, and a continuous infusion is required to maintain them. The transient hemodynamic effects of nitroprusside are confirmed in our study. In addition, our results indicate that prazosin produces hemodynamic effects in refractory heart failure similar to those of nitroprusside, including a reduction in systemic vascular resistance, an increase in cardiac output and a decrease in left ventricular filling pressure. In the dosage used, pulmonary arterial pressures and vascular resistance decreased and left ventricular stroke work index increased significantly; these effects are similar to those seen with nitroprusside

and occurred in association with a reduction in heart rate-systolic arterial pressure product, implying that myocardial oxygen consumption did not increase.[19]

Effects of prazosin: Prazosin has been shown to be an effective vasodilator agent by its direct action on vascular smooth muscle through inhibition of phosphodiesterase and increase in the level of cyclic adenosine monophosphate (AMP).[15,20–22] Some of its vasodilator actions have been attributed to mild alpha blocking properties and can be blocked by alpha adrenergic agonists.[15] It has been reported that vasodilation produced by prazosin does not result in tachycardia because in therapeutic dose the drug increases myocardial cyclic guanine monophosphate (GMP), thus attenuating the chronotropic augmentation.[22] This appears to be advantageous because most of the commonly used vasodilators like hydralazine result in reflex tachycardia when given to normotensive or hypertensive subjects.[23] Indeed, our study shows that in spite of a reduction in arterial pressure, no change in heart rate was seen. Lack of a reflex tachycardia response in patients with heart failure given vasodilators has also been attributed to attenuated baroreceptor responses in the heart failure state.[24,25]

In the absence of direct inotropic actions,[15] the exact mechanism for the increase in cardiac output after the administration of prazosin is not known. As a working hypothesis, others have suggested that cardiac output increases secondary to increased myocardial fiber shortening as a result of reduced ventricular load[26] in heart failure when vasodilator agents are given.[27] In this regard, the decrease in systemic vascular resistance as observed with other afterload-reducing agents[1–6] provides evidence for reduction of at least one component of the ventricular load during ejection. Whatever the precise mechanism of action in patients with heart failure, prazosin in the doses used improves left ventricular performance, clinically and hemodynamically (Fig. 2 and 3), without producing tachycardia. The decrease in arterial pressure is only slight and unlikely to result in deterioration of end-organ perfusion. The decline in pulmonary arterial pressures and vascular resistance observed with prazosin is probably due to direct venodilator action or secondary to increased cardiac output, or both. The exact mechanism and the role of increased cardiac output in decreasing vascular resistance are not clear.

Left ventricular stroke work increased significantly in our patients. As observed with other vasodilator regimens,[1–6,9,27] it is conceivable that the improvement in left ventricular stroke work occurred solely as a result of decreased systemic vascular resistance. It is unlikely that myocardial oxygen demand increased because heart rate-systolic arterial pressure product was unaltered. In fact, a decrease in this product observed in our patients suggests a reduced oxygen demand.

Nitroprusside versus prazosin: Hemodynamic alterations produced by nitroprusside infusion were used as the "standard" to evaluate the hemodynamic effects of prazosin. The effects of these two agents are qualitatively but not quantitatively similar (Fig. 4). The same decrease in arterial pressure results in a greater increase in left ventricular stroke work with nitroprusside. Nitroprusside also produces a greater decrease in left ventricular filling pressure and pulmonary arterial pressure, even though resistance values in the systemic and pulmonary vascular beds decrease equally.

Left ventricular function relating left ventricular stroke work index with filling pressure (Fig. 5) shows greater improvement with nitroprusside. It is possible that nitroprusside has more potent vasodilator action or the dose of prazosin was small or nitroprusside has other unexplained actions.

Therapeutic implications: These hemodynamic data suggest that prazosin has beneficial effects in certain patients with heart failure who respond to intravenous nitroprusside infusion. The improvement in clinical status seen in these patients appears promising. The absence of significant side effects with prazosin reported earlier in a clinical setting[28] and in our study warrants a long-term trial in patients with heart failure who have low stroke volume and high left ventricular filling pressure. To ensure clinical safety, the dose should be small initially (2 mg four times daily) and then increased to 4 or 5 mg four times daily.

Acknowledgment

We acknowledge the expert secretarial assistance of Deborah Coker.

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Effect of Sublingual Nitroglycerin in Emergency Treatment of Severe Pulmonary Edema

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Twenty-two patients with clinical signs of pulmonary edema (orthopnea, cyanosis, profuse sweating and pulmonary rales*) were studied and separated into two groups. In seven patients (Group A), hemodynamic studies were performed. Pulmonary arterial pressure and cardiac output were measured during the emergency condition of severe pulmonary edema. Within 10 minutes after sublingual administration of nitroglycerin, 1.6 mg, left ventricular filling pressure decreased from 33 ± 10 (mean ± 1 standard deviation) to 24 ± 8 mm Hg, and cardiac output increased significantly from 3.3 ± 0.8 to 3.7 ± 0.8 liters/min. In one patient with recent myocardial infarction, left ventricular filling pressure decreased from 50 to 27 mm Hg within 5 minutes. Orthopnea and pulmonary rales disappeared rapidly.

In 15 patients (Group B), the clinical course was observed and documented. These patients received one to six doses of 0.8 to 2.4 mg of nitroglycerin sublingually at intervals of 5 to 10 minutes. Five minutes after administration, the first evidence of clinical improvement was observed in seven of these patients. After 15 to 20 minutes, pulmonary rales disappeared or decreased in 11 and dyspnea decreased in 14. The elevated arterial blood pressure and heart rate decreased significantly. Only one patient with terminal pulmonary edema remained refractory to therapy. Thus, sublingual nitroglycerin had beneficial effects in the emergency treatment of classic pulmonary edema. Elevated left ventricular filling pressure decreased and cardiac output increased within 5 minutes. These hemodynamic changes produced immediate clinical improvement.

Recent clinical and experimental studies have documented the beneficial hemodynamic effect of nitroglycerin in left ventricular failure after acute myocardial infarction.[1–16] However, whether nitroglycerin is also beneficial in the most serious form of left ventricular failure, severe pulmonary edema,[17] has not been systematically studied. The aim of treatment of pulmonary edema is the immediate reduction of left ventricular filling pressure and arterial blood pressure, which in most cases are elevated.[15]

Methods

Twenty-two patients with severe pulmonary edema were studied and separated into two groups: Group A comprised seven patients with pulmonary edema whose pulmonary arterial pressure and cardiac output were measured before and during nitroglycerin therapy. Group B consisted of 15 patients whose clinical symptoms and findings were documented before and during nitroglycerin therapy.

Group A

In these seven patients, systolic, diastolic (that is, left ventricular filling pressure) and mean pulmonary arterial pressures and cardiac output were measured during severe pulmonary edema. Blood pressure was taken with use of a cuff sphygmomanometer and stethoscope.

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* Throughout this article the term pulmonary rales refers to "distance" rales, that is, loud rales heard by the examiner without a stethoscope at a distance from the patient.

TABLE I

Hemodynamic Effects of Sublingual Nitroglycerin in Seven Cases of Severe Pulmonary Edema (Group A)

Case no.	Diagnosis	Control				3 Minutes				5 Minutes				10 Minutes			
		PASP	LVFP	$\overline{PA}$	CO	PASP	LVFP	$\overline{PA}$	CO	PASP	LVFP	$\overline{PA}$	CO	PASP	LVFP	$\overline{PA}$	CO
1	Recent anterior wall infarction	54	25	33	3.96	45	15	30	3.63	48	15	27	3.72	45	17	32	4.55
2	CHD, condition after infarction	60	40	48	2.07	50	45	40	2.28	55	35	43	2.45	55	35	43	2.47
3	Recent posterior wall infarction, condition after cardiac arrest	85	50	65	3.60	60	33	45	4.20	50	28	38	4.11	48	27	38	4.33
4	CHD, condition after infarction	45	22	33	4.13	33	11	21	3.98	33	11	21	3.79	36	13	23	4.10
5	CHD, condition after infarction	70	35	48	2.57	65	27	40	2.68	60	26	38	2.74	68	25	36	2.87
6	Recent infarction, condition after ventricular fibrillation	62	26	42	3.93	50	18	27	3.91	48	17	30	3.93	52	20	34	4.08
7	CHD, condition after infarction	65	35	50	3.02	65	28	43	3.43	63	30	45	3.40	65	33	47	3.80
	Mean	63	33	46	3.32	53	25	35	3.44	51	23	35	3.44	53	24	36	3.74
	SD	13	10	11	0.8	12	12	9	0.7	10	9	9	0.6	12	8	8	0.8
	P value*	...	...	...	...	<0.02	<0.02	<0.005	<0.3	<0.05	<0.01	<0.001	<0.3	0.1	<0.02	<0.005	<0.01

* Compared with control values. CHD = coronary heart disease; CO = cardiac output (liters/min); LVFP = left ventricular filling pressure (mm Hg); PASP = mean pulmonary arterial systolic pressure (mm Hg); PA = mean pulmonary arterial pressure (mm Hg).

Cardiac output was generally determined with the thermodilution technique, using a no. 7F Swan-Ganz flow-directed thermodilution catheter. In some cases, it was determined according to the Fick principle with measurement of arteriovenous oxygen difference, hemoglobin and oxygen consumption. Values were obtained before administration of nitroglycerin and thereafter at intervals of 3, 5, 10 and in some cases 30 minutes.

Three of the seven patients in Group A had had a recent myocardial infarction and four had acute left ventricular failure after infarction (Table I). All seven received a single dose of nitroglycerin sublingually; none received morphine, digitalis or diuretic agents before, during or after nitroglycerin therapy. No respiratory support with or without positive pressure ventilation was necessary. All patients received simple supportive measures including nasal administration of oxygen and use of a heart bed that permitted elevation of the patient's head and lowering of the limbs.

Group B

In these 15 patients, the clinical findings, heart rate and blood pressure were recorded before sublingual administration of nitroglycerin and thereafter at intervals of 5, 10, 15 to 20, 30, 60 and 120 minutes. The severity of dyspnea and cyanosis and bouts of profuse sweating as well as the severity and extent of pulmonary rales were documented.

Four patients in Group B had coronary artery disease, one a valve defect, five a recent myocardial infarction, two myo-

TABLE II

Effect of Sublingual Nitroglycerin in 15 Cases of Severe Pulmonary Edema: Clinical Protocol (Group B)

Case no.	Diagnosis	Grade of Pulmonary Edema	Sublingual Nitroglycerin (mg)							Clinical Findings				
			0 Min	5 Min	10 Min	15 Min	20 Min	25 Min	30 Min	5 Min	10 Min	15–20 Min	30 Min	60–120 Min
1	CHD	IV	2.4	1.6						++++	+++	+	+	0
2	MVR	IV	2.4							++++	++	++	++	+
3	CHD	IV	1.6	1.6	1.6	1.6	1.6	1.6	1.6	++++	+++	+++	++	+
4	CHD	III	0.8							++++	++++	++	+	+
5	AMI	III	1.5*	6*	3*	4*				++++	++++	+++	++	0
6	COCM	IV	0.8	0.8	0.8	0.8				+++	++	+	+	0
7	AMI	IV	1.6		0.8	0.8				+++	++	++	+	+
8	HHD	III	0.8			0.8		0.8	1.6	++++	++++	++++	+++	+++
9	UPE	III	0.8			0.8				++++	++++	+++	++	+
10	COCM	IV	1.6							+++	+++	+	0	0
11	HHD	I	1.6	1.6	1.6					++++	+	+	+	+
12	AMI	II	1.6	1.6	1.6					+++	+++	++	0	0
13	AMI	II	1.6	1.6		0.8				+++	+	+	0	0
14	AMI	II	0.8		1.6					+++	+	+	++	0
15	CHD	II	0.8	0.8	0.8	0.8	0.8			++	+	+	0	0

* Intravenously administered (mg/hr).
++++ = no change; +++ = slight improvement; ++ = decreased pulmonary rales; + = no pulmonary rales; 0 = free of symptoms.
AMI = acute myocardial infarction; CHD = coronary heart disease; COCM = congestive cardiomyopathy; HHD = hypertensive heart disease; MVR = mitral valve replacement; UPE = unknown origin of pulmonary edema.

cardial disease, two "decompensated hypertension" and one pulmonary edema of unknown origin (Table II).

These 15 patients were generally in the typical heart bed, as required by their condition, and received oxygen by nose. No digitalis was administered before or during treatment with nitroglycerin. Five patients had previously been treated with furosemide without a reduction of pulmonary edema. Two patients had received 10 mg of morphine 1 hour before the administration of nitroglycerin but had shown no improvement.

Fourteen of the 15 patients in this group were given one to six doses of 0.8 to 2.4 mg of nitroglycerin sublingually at intervals of 5 to 10 minutes (one to three capsules of Nitrolingual rot®, manufactured by Fa. Pohl Boskamp, Hohenlockstedt/Holstein). The initial dose was 0.8 mg in six patients, 1.6 mg in six patients and 2.4 mg in two patients. All but three patients needed additional doses of nitroglycerin, and three patients also received nitroglycerin intravenously (1 percent nitroglycerin solution, Fa. Merck, Darmstadt). One patient (Case 5) received nitroglycerin only intravenously.

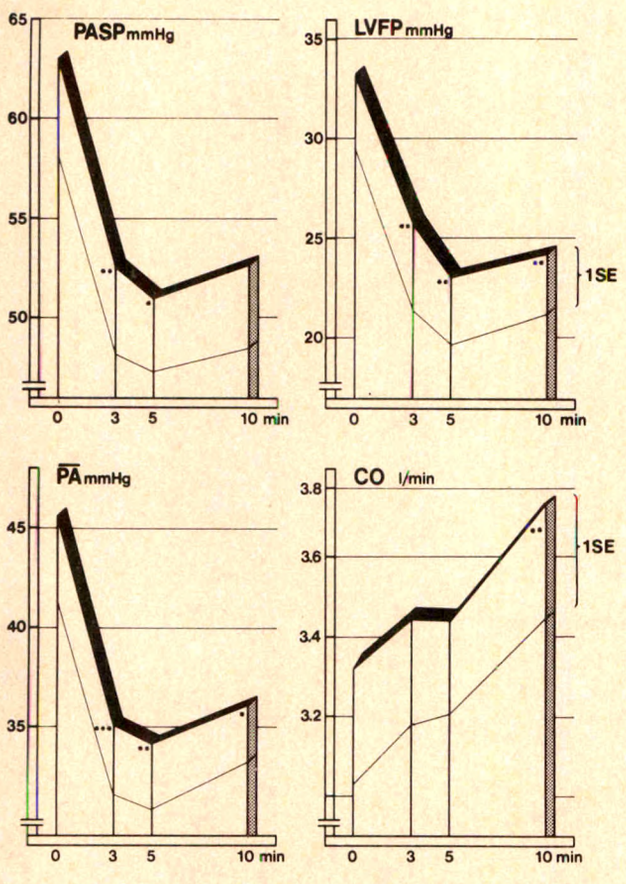
Student's t test for paired and unpaired data was used for all statistical calculations. The criterion of significance was a probability (P) value of <0.05.

Results

Hemodynamic Measurements (Group A)

In seven patients pulmonary arterial pressure and cardiac output were measured during pulmonary edema (Table I, Fig. 1). Sublingual nitroglycerin significantly decreased pulmonary arterial pressure within 5 minutes: Systolic pulmonary arterial pressure decreased from 63 ± 13 to 51 ± 10 mm Hg (mean ± 1 standard deviation), diastolic pressure decreased from 33 ± 10 to 24 ± 8 mm Hg and mean pressure decreased from 46 ± 11 to 35 ± 9 mm Hg; pulmonary arterial wedge pressure decreased from 30 ± 16 to 21 ± 8 mm Hg. Five to 10 minutes after administration of nitroglycerin, the reduced pressure increased slightly (Fig. 1). Cardiac output increased significantly from 3.3 ± 0.8 to 3.7 ± 0.8 liters/min (10th minute). Arterial blood presssure decreased from 128/90 to 122/75 mm Hg.

Distinct improvement was noted in a 68 year old patient with recent inferior wall infarction and pulmonary edema (Fig. 2). Pulmonary arterial pressure was drastically reduced



• p<0.05 •• p<0.02–0.01 ••• p<0.005–0.001

FIGURE 1. Hemodynamic measurements in seven patients with severe pulmonary edema (Group A). After a single sublingual dose of 1.6 mg of nitroglycerin, left ventricular filling pressure (LVFP) decreased from 33 to 24 mm Hg and cardiac output (CO) increased from 3.3 to 3.7 liters/min within 5 to 10 minutes. l = liters; p = probability; PA = mean pulmonary arterial pressure; PASP = pulmonary arterial systolic pressure; SE = standard error.

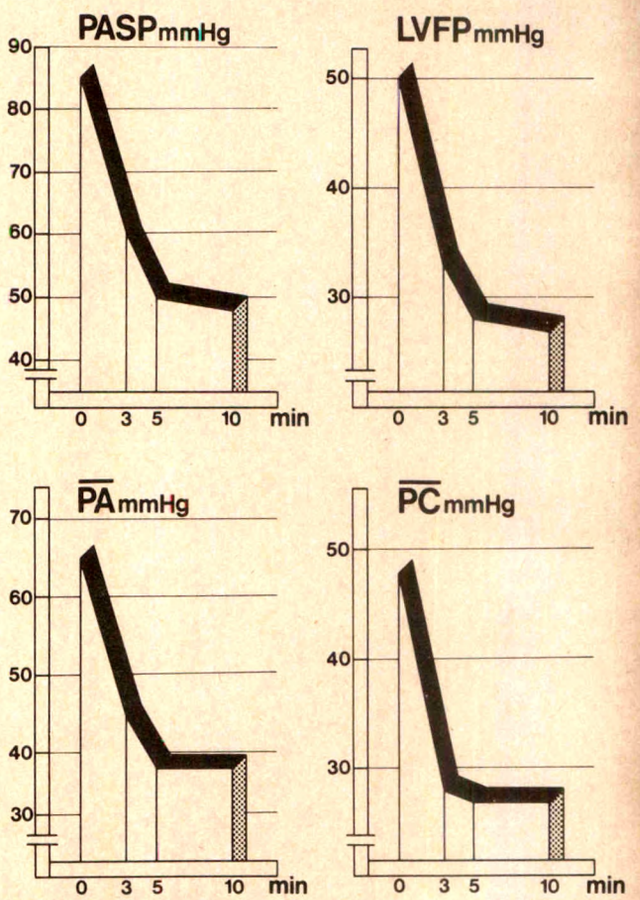


FIGURE 2. In a 68 year old patient with recent myocardial infarction and severe pulmonary edema a single sublingual dose of 0.8 mg of nitroglycerin rapidly decreased the pulmonary arterial pressure. Left ventricular filling pressure (LVFP) decreased from 50 to 27 mm Hg within 5 minutes. The patient's condition improved rapidly, dyspnea immediately decreased and rales disappeared. PASP = pulmonary arterial systolic pressure; PA = mean pulmonary arterial pressure; PC = mean pulmonary capillary wedge pressure.

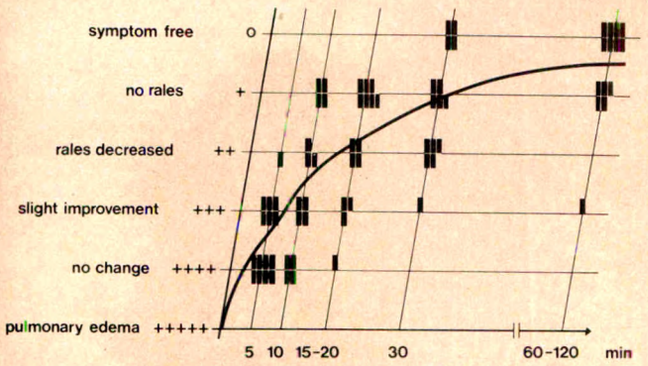


FIGURE 3. Clinical course of 15 patients with severe pulmonary edema (Group B) during the first 60 to 120 minutes of nitroglycerin therapy. Each patient **(closed rectangles)** is classified according to clinical findings at each time interval. The **solid curve** denotes the change of mean improvement at a given time interval.

by administration of 0.8 mg of sublingual nitroglycerin. Systolic pulmonary arterial pressure decreased from 85 to 48 mm Hg, left ventricular filling pressure from 50 to 27 mm Hg, mean pulmonary arterial pressure from 65 to 38 mm Hg and pulmonary arterial wedge pressure from 48 to 27 mm Hg. The clinical findings improved accordingly. The initially extremely severe orthopnea and the audible pulmonary rales diminished within 5 minutes and disappeared almost completely after 10 minutes.

Clinical Record (Group B)

All patients of Group B had clinical signs of pulmonary edema, such as severe orthopnea, cyanosis, pulmonary rales and profuse sweating. The diagnoses and clinical findings before and after therapy are listed in Table II. The pulmonary edema was graded in four classes according to clinical signs:

Grade I (*prepulmonary edema*): Mild pulmonary edema with pronounced dyspnea, mild rhonchi and numerous moist rales (one patient).

Grade II (*pulmonary edema*): Edema of moderate severity with relatively loud rales, audible at the patient's mouth, and mild orthopnea (four patients).

Grade III (*severe pulmonary edema*): Severe edema with orthopnea and pronounced pulmonary rales (four patients).

Grade IV (*severest pulmonary edema or "classic" pulmonary edema*): Orthopnea, profuse sweating, loud rales (six patients).

Fourteen of the 15 patients studied showed clinical improvement after administration of nitroglycerin. One patient had a slight temporary improvement. Eight patients became free of symptoms (Table II).

After 5 minutes, initial improvement was observed in seven patients; in one patient, the rales had already diminished (Fig. 3). After 10 minutes, four other patients showed initial improvement. Hence, 11 of 15 patients showed improvement within 10 minutes.

After 15 to 20 minutes further improvement was noted. Rales disappeared in 7 of the 15 patients and diminished in 4. An initial decrease in dyspnea occurred in three patients who had previously been refractory to therapy. Thus, improvement of various degrees was observed in 14 of 15 patients (Fig. 3).

After 30 minutes four patients were free of symptoms, five had no rales, and in five other patients the rales still were decreasing. All but 1 of the 15 patients manifested clinical improvement of at least two grades.

One to 2 hours after the onset of therapy, eight patients were completely free of symptoms, and in five other patients the rales had further diminished. All but one patient had shown improvement of three to four grades.

The time-dependent improvement of 10 patients with severe (grades III and IV) pulmonary edema was compared with the improvement of the five patients with mild edema (grades I and II) (Fig. 4). The five patients with mild edema showed more rapid improvement than those with severe edema. In four of the five, rales disappeared after 10 minutes; after 30 minutes, three patients were free of symptoms. By comparison, only 3 of the 10 patients with grades III and IV pulmonary edema had disappearance of rales after 10 minutes and only 1 was free of symptoms after 30 minutes.

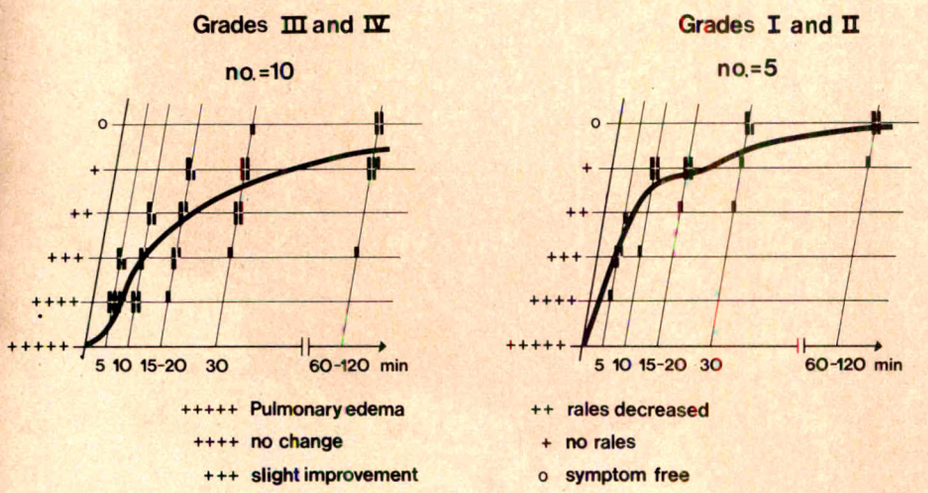


FIGURE 4. Five patients with mild (grades I and II) pulmonary edema **(right panel)** had more rapid improvement than the 10 with severe (grades III and IV) pulmonary edema **(left panel)**. Note the steep increase in mean improvement in the **right panel.** Symbols as in Figure 3.

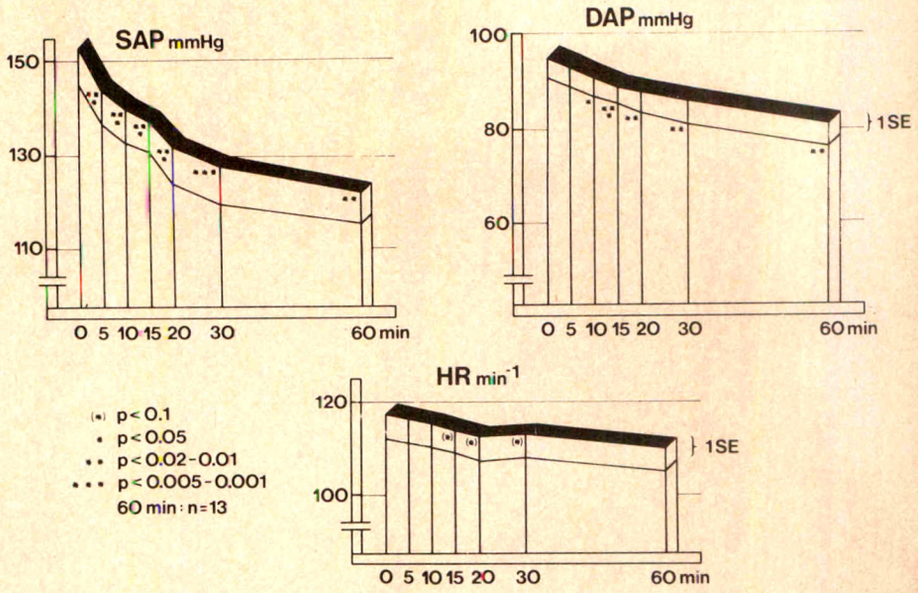


FIGURE 5. Effect of repeated nitroglycerin administration on arterial blood pressure and heart rate in 15 patients with pulmonary edema (Group B). Systolic (SAP) and diastolic (DAP) arterial pressure decreased significantly shortly after administration of nitroglycerin. Heart rate (HR) tended to decrease during treatment. n = number of patients; p = probability; SE = standard error.

The reduction in systolic blood pressure was more pronounced than the reduction in diastolic blood pressure (Fig. 5). Within the first 10 minutes, systolic pressure decreased significantly from 153 ± 31 mm Hg to 140 ± 29 mm Hg. After 60 minutes, both systolic and diastolic blood pressures had decreased from 153 ± 31/95 ± 16 to 122 ± 28/82 ± 17 mm Hg. During therapy, heart rate decreased slightly.

In all patients, the initially elevated blood pressure decreased and subsequently remained within normal limits. One patient, a 64 year old woman, was an exception. Clinically, she presented with the full clinical findings of pulmonary edema, had extensive rales and typical butterfly-shaped lung spots on X-ray examination. Her blood pressure decreased from 160/80 to 90/60 mm Hg after two doses of nitroglycerin. However, the arterial hypoxia with partial pressure of oxygen of 40 mm Hg made oxygen administration necessary. The patient's condition was later diagnosed as Goodpasture syndrome with multiple lung hemorrhages.

Discussion

Hemodynamics and clinical effects of nitroglycerin therapy: The main objective in treating severe pulmonary edema is to provide immediate relief of this threatening condition by reducing left ventricular filling pressure as assessed with the pulmonary capillary wedge pressure. Within the first 3 to 5 minutes after administration of nitroglycerin, a marked decrease of diastolic pulmonary arterial pressure was noted. Cardiac output increased significantly. The reduction of abnormally increased filling pressures induced the increase in cardiac output.[4–8,14–16]

During therapy, clinical improvement after 10 minutes was observed in 11 of 15 patients. This finding correlated with the reduction in pulmonary arterial pressure after 5 minutes. Our hemodynamic and clinical findings demonstrate the rapid effect of nitroglycerin in cases of pulmonary edema.

The patients' clinical status during pulmonary edema was relatively stable before the start of nitroglycerin therapy. No spontaneous recovery was observed with use of supportive measures such as the heart bed or nasally administered oxygen. None of the patients needed respiratory support with or without positive pressure ventilation. The rapid hemodynamic improvement was attributed to nitroglycerin alone because no other mechanical or pharmacologic interventions were used. Pulmonary arterial wedge pressure decreased by 50 percent of the control levels within 2 to 3 minutes.

In our study nitroglycerin was used alone. However, the data gathered should make it easier to assess whether in a given situation nitroglycerin should be used alone or as a complement to other traditional therapy.

Possible limitations or dangers of therapy: In patients with hypotension, administration of nitroglycerin may be detrimental because reduction of coronary perfusion pressure may enhance myocardial ischemia. In patients whose systolic arterial pressure is less than 100 mm Hg, nitroglycerin can only be used in very small doses or, in combination with dopamine, to induce arterial vasoconstriction. In addition, nitroglycerin seems to be ineffective in terminal myocardial disease or severe cardiogenic shock.

Mechanism of therapeutic effect: The main action of nitroglycerin is a result of its influence on the peripheral venous system.[2,3,17,18] Nitroglycerin causes a dilatation of the venous system and a decrease in left ventricular filling pressure.[15] Moreover, because the arterioles are dilated, otherwise hypertensive blood pressure levels are lowered. The decreased pressure causes a reduction of left ventricular impedance and therefore alleviates the stroke work of the heart. Hence, a decrease in ventricular end-diastolic pressure may also be due to this mechanism.[19]

Implications: The standard treatment of pulmonary edema, using morphine, furosemide and digitalis should not be replaced by nitroglycerin therapy. The objective of our study was to document the effects of nitroglycerin as a single drug in the emergency treatment of pulmonary edema. Nitroglycerin produced immediate clinical improvement by decreasing left ventricular filling pressure within 5 minutes of its administration. Phlebotomy can be avoided because of the drug's "internal bleeding" effect.

Acknowledgment

Preliminary data and Figure 2 were previously published in the European Journal of Cardiology.[15]

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Left Ventricular Dynamics During Long-Term Digoxin Treatment In Patients With Stable Coronary Artery Disease

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Ten patients with stable coronary artery disease who did not have clinical congestive heart failure and had recovered (3 or more months) from coronary bypass graft surgery were given both intravenous and oral digoxin. Left ventricular performance was assessed weekly for 3 control weeks, during 4 weeks of long-term oral digoxin treatment, and during 2 to 3 weeks of recovery. Serial noninvasive measurements of velocity of circumferential fiber shortening, ejection fraction, end-diastolic volume and cardiac output were obtained with computer-assisted fluoroscopic analysis of the motion of surgically implanted mid wall myocardial markers that outline the left ventricular cavity. During 4 weeks of oral digoxin therapy, mean serum digoxin levels were maintained between 1.2 ± 0.1 and 1.4 ± 0.1 ng/ml (mean ± standard error of the mean). Mean velocity of circumferential fiber shortening increased 15.6 percent from 0.65 ± 0.05 to 0.75 ± 0.05 circumferences/sec ($P < 0.001$) and ejection fraction increased 8.5 percent from 0.51 ± 0.03 to 0.55 ± 0.03 ($P < 0.001$). End-diastolic volume and cardiac output were not changed significantly. The inotropic response to oral digoxin was similar during the 4th week of treatment to that seen during the first week, and the mean inotropic effect of chronic oral digoxin was not significantly less than that achieved by administration of 1 mg intravenously over 15 minutes. These data suggest that chronic oral digoxin treatment exerts a sustained inotropic effect on the nonfailing heart that persists for at least 4 weeks and is equivalent to that achieved with rapid intravenous digitalization.

Although both the acute inotropic effect of digitalis and its chronotropic effect in the presence of atrial fibrillation have been well documented in man,[1–4] it has been difficult to quantitate the effect of long-term oral digoxin therapy on ventricular performance in patients without overt heart failure. Previous studies that evaluated cardiac performance using clinical criteria and ballistocardiography,[5] systolic time intervals,[6–9] videotracking[10] and echocardiography[11] yielded conflicting results, were studies of short duration or examined limited portions of the ventricular wall. To overcome some of the methodologic problems encountered during previous investigations, we assessed left ventricular function with computer-assisted fluoroscopic analysis of recordings of the motion of surgically implanted mid wall markers that outline the left ventricular cavity. This noninvasive technique allowed repeated accurate measurements of ventricular performance.

The current study was designed to investigate the long-term effects of digoxin on left ventricular performance in patients with stable compensated coronary artery disease, and to compare the inotropic effect of acute digitalization with that obtained with long-term drug administration.

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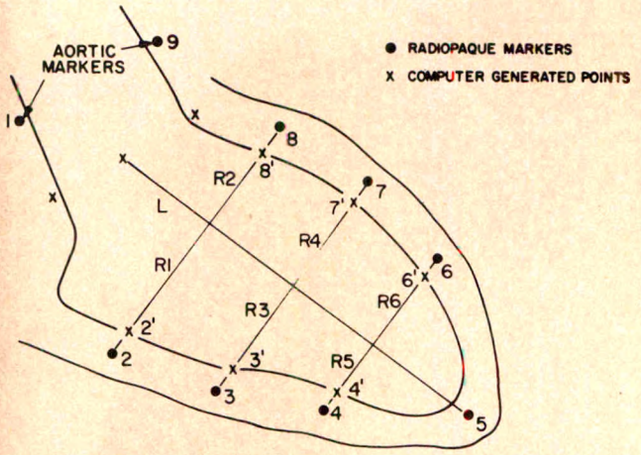


FIGURE 1. Schematic diagram demonstrating the location of radiopaque intramyocardial markers that outline the left ventricular cavity in the right anterior oblique projection. R1-R6 represent perpendicular lines connecting individual markers with the long ventricular axis (L). (Reprinted with permission of Alderman et al. and Computers in Cardiology.[14])

Methods

Patients: Ten patients, aged 41 to 60 years, who had had left ventriculography, coronary arteriography and coronary bypass graft surgery 4 to 29 months earlier participated in the study. Informed consent was obtained from each patient. Baseline data, including physical examination, electrocardiogram and determinations of serum electrolyte and blood urea nitrogen were performed. No patient had symptoms of congestive heart failure or was taking digitalis; two patients were using diuretic drugs. Two of the 10 patients had mild angina pectoris, 4 had prior myocardial infarction and 7 had preoperative segmental wall motion abnormalities.

At the time of cardiac surgery, each patient had seven tantalum coils (1.5 mm by 0.6 mm) implanted at a depth of 5 mm into the left ventricular wall and two tantalum clips affixed to the aorta 3 cm above the level of the aortic valve (Fig. 1) to outline the left ventricular cavity in the 30° right anterior oblique projection. Markers were inserted with generally equal spacing into the anterior and inferior myocardium regardless of whether the wall appeared normal or abnormal.

Measurements of left ventricular performance: Ventricular function was evaluated fluoroscopically by recording the motion of these markers on a video disk at 30 frames/sec during suspended mid inspiration. Particular care was taken to avoid the Valsalva maneuver. Before study, each patient rested in the X-ray cradle for a minimum of 10 minutes or until heart rate and blood pressure were stable. Systolic ventricular wall motion was analyzed by digitizing the X-Y coordinates of each marker every 33 msec using a light pen system as previously described.[12–14] Mean ventricular hemidiameter was derived every 33 msec by averaging the lengths of six perpendicular lines connecting the anterior and inferior markers to the long ventricular axis, defined as the line from the mid aortic plane to the apical marker. Analysis of these data allowed measurement of mean velocity of circumferential fiber shortening, ejection fraction, end-diastolic volume, heart rate and cardiac output. Ventricular volumes were calculated with the single plane area-length method of Dodge and Sandler[15] and corrected for the volume of muscle included within the markers, using a regression equation previously reported.[13] Velocity of circumferential fiber shortening was computed as the normalized mean shortening rate of the ventricular diameter from end-diastole to 167 msec after the occurrence of maximal end-diastolic diameter.

Protocol: Patients were studied weekly at the same time of day for 9 consecutive weeks. In most patients, data from nine cardiac cycles were analyzed and averaged each week. Control measurements were obtained for a minimum of 3 weeks. After the final control data were recorded, 1 mg of digoxin in a small volume of dextrose solution was given intravenously over a period of 15 minutes, and fluoroscopic measurements were repeated 1.5 hours later.

After this acute digitalization, each patient took oral digoxin daily for 4 weeks. Measurements of left ventricular performance were repeated weekly, 8 to 12 hours after the last oral digoxin dose. Serum digoxin levels were measured concurrently and doses were adjusted to keep serum levels between 1.0 and 2.0 ng/ml. This required a daily intake of between 0.375 mg and 0.625 mg of digoxin. At the end of 4 or more weeks of long-term digoxin therapy, the drug was discontinued and ventricular performance was measured for an additional 2 week recovery period. No untoward side effects were noted during this study. Values presented for the acute digitalization study are the mean of measurements obtained from four to nine cardiac cycles recorded immediately before and 1.5 hours after intravenous digoxin administration. Results of the long-term study are averages of values obtained from all weeks within a given study period, that is, control period, period of

TABLE I

Effect of Digoxin on Left Ventricular Performance in 10 Patients

		Digoxin Administration					
	Control*	Short-Term*	(*P*)	Long-Term*	(*P*)	Recovery†	(*P*)
VCf	0.67 ± 0.06	0.78 ± 0.06	(<0.001)	0.75 ± 0.05	(0.001)	0.67 ± 0.05	(NS)
EF	0.50 ± 0.03	0.53 ± 0.03	(<0.05)	0.55 ± 0.03	(<0.001)	0.51 ± 0.03	(NS)
EDV	135 ± 13	132 ± 12	(NS)	137 ± 20	(NS)	147 ± 17	(NS)
CO	4.6 ± 0.4	4.2 ± 0.3	(<0.05)	4.3 ± 0.5	(NS)	4.6 ± 0.4	(NS)
HR	69.7 ± 4	62.8 ± 5	(<0.001)	62 ± 2.9	(<0.05)	66 ± 3.0	(NS)
BP	109 ± 5.6	123 ± 6.3	(<0.01)	113 ± 5.3	(NS)	109 ± 5.4	(NS)

* Control values are mean values for 3 weeks (four to nine cardiac cycles per patient per week; short-term digoxin values are mean values of four to nine cardiac cycles per patient; long-term digoxin values are mean values for 4 weeks (four to nine cardiac cycles per patient per week).

† Recovery values are mean values for 2 to 3 weeks (four to nine cardiac cycles per patient per week).

BP = systolic blood pressure (mm Hg); CO = cardiac output (liters/min); EDV = end-diastolic volume (ml); EF = ejection fraction (%); HR = heart rate (beats/min); NS = not significant; *P* = probability values (comparison with control measurements); VCf = velocity of circumferential fiber shortening (circumferences/sec).

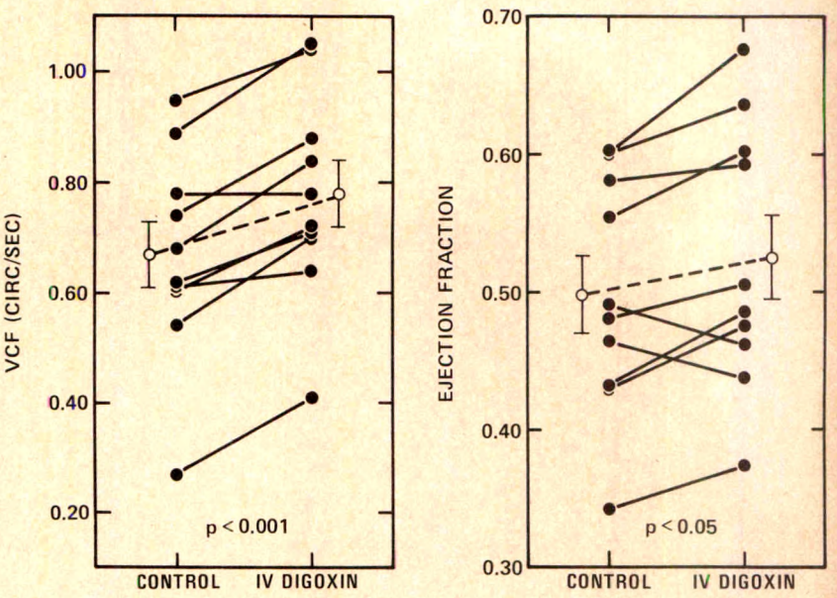


FIGURE 2. Values for velocity of circumferential fiber shortening (VCF) (**left**) and ejection fraction (**right**) for individual patients (**closed circles**) and the group (**open circles**) immediately before and 1.5 hours after the administration of 1 mg of digoxin intravenously. Individual points represent the mean of four to nine cardiac cycles per patient. Brackets indicate standard error. CIRC = circumferences; IV = intravenous; p = probability.

oral drug administration and period of recovery. Data were analyzed by paired and unpaired t tests where appropriate.

Results

Acute intravenous digoxin administration: The results of short-term intravenous and long-term digoxin administration, and of the recovery period after digoxin therapy are summarized in Table I. The short-term (1.5 hours) effects of 1 mg of intravenous digoxin on velocity of circumferential fiber shortening and ejection fraction are shown in Figure 2. The velocity of circumferential fiber shortening increased by an average of 19 percent (P <0.001) and was greater in 9 of 10 patients. Ejection fraction also increased acutely in 8 of 10 patients, and for the group increased 4.5 percent from a mean of 0.50 ± 0.03 to 0.53 ± 0.03 (P <0.05). Mean systolic blood pressure increased 14 mm Hg, end-diastolic volume was unchanged, heart rate decreased 7 beats/min and cardiac output decreased slightly (Table I).

Long-term oral digoxin therapy: The mean values of velocity of circumferential fiber shortening and ejection fraction during the initial 3 to 4 week control period, during 4 weeks of oral digoxin therapy, and during the subsequent recovery period are shown in Figure 3 for individual patients and for the entire group. The mean velocity of circumferential fiber shortening

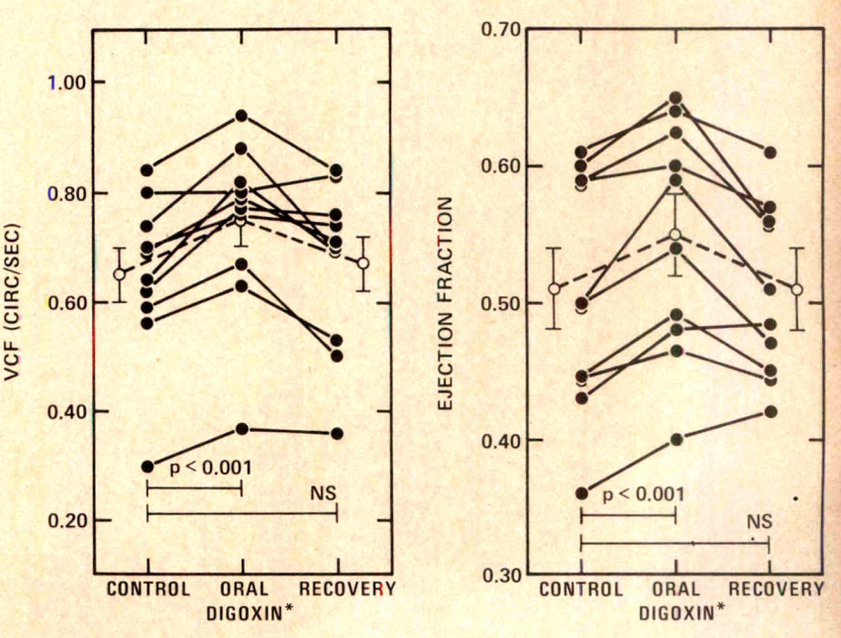


FIGURE 3. Mean response of velocity of circumferential fiber shortening (VCF) (**left**) and ejection fraction (**right**) for individual patients (**closed circles**) and the group (**open circles**) during the 3 week control and 2 week recovery periods and during 4 weeks of oral digoxin treatment. Data from four to nine cardiac cycles per week per patient were averaged for the appropriate periods. Brackets indicate standard error. NS = not statistically significant.

*MEAN OF 4 WEEKS

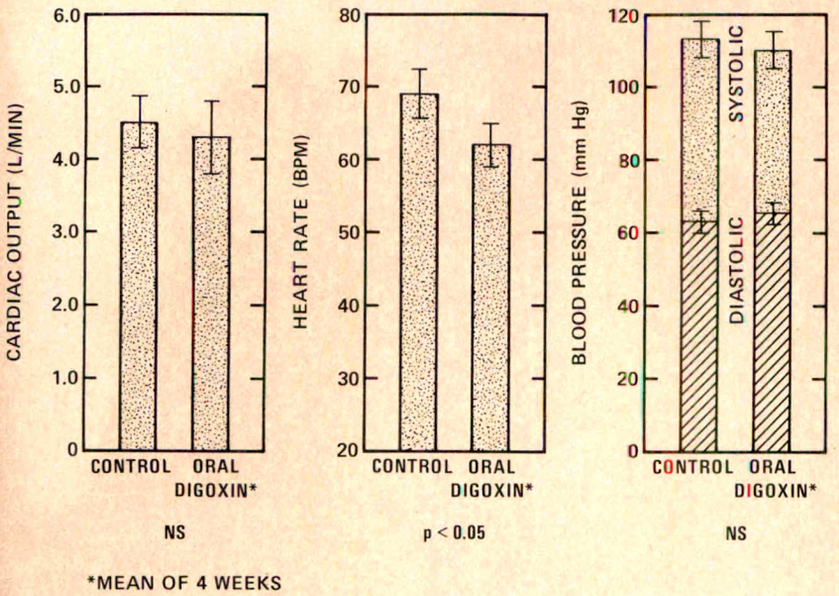


FIGURE 4. Mean group values of cardiac output, heart rate and blood pressure during the 3 week control period and 4 weeks of oral digoxin therapy. BPM = beats/min; L = liters; NS = not statistically significant; p = probability.

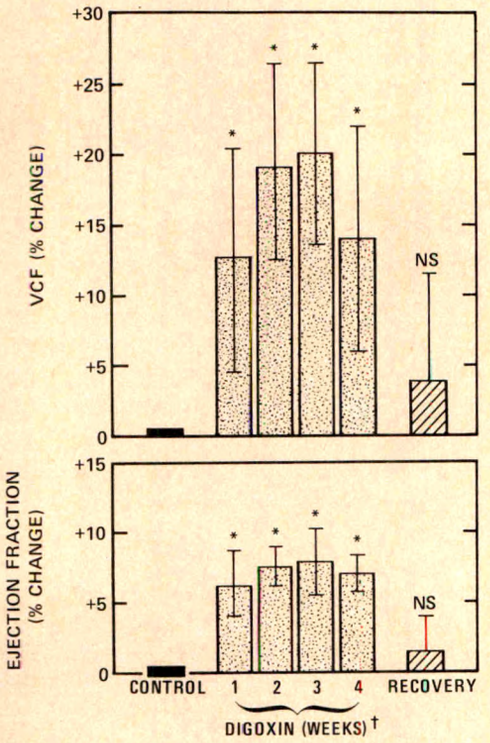
and ejection fraction increased significantly over the 4 week study period relative to the preceding control period ($P < 0.001$). The velocity of circumferential fiber shortening increased in 9 of 10 patients and ejection fraction increased in all patients. The average increases were 15.6 ± 2.6 percent in velocity of circumferential fiber shortening (from 0.65 ± 0.05 to 0.75 ± 0.05 circumferences/second) and 8.5 percent ± 1.4 percent in ejection fraction (from 0.51 ± 0.03 to 0.55 ± 0.03). In addition, no significant difference between the control and recovery levels of either measurement was present, suggesting that the effects observed were reversible and temporally related to drug administration. Cardiac output, end-diastolic volume and systolic blood pressure were not significantly altered by long-term drug administration. However, average heart rate decreased from 69 ± 3.2 to 62 ± 2.9 beats/min ($P < 0.05$) (Fig. 4).

Measurements for each week of digoxin administration: In order to examine more closely the response to continuing oral digoxin treatment, the mean levels of velocity of circumferential fiber shortening and ejection fraction for each week of drug administration were normalized relative to their values during the control period. The results, expressed as percent change from control, are shown in Figure 5. Serum digoxin levels for the group averaged between 1.2 ± 0.1 and 1.4 ± 0.1 ng/ml. During each week of treatment, the mean velocity of circumferential fiber shortening remained elevated by 12 to 20 percent over control levels, and mean ejection fraction was augmented 6 to 8 percent (all differences significant, $P < 0.05$). Although Figure 5 suggests a trend toward diminished drug effect during the 4th week of drug treatment compared with earlier weeks, the change was not statistically significant. In addition, comparison of the effects of short-term digoxin administration with those of long-term oral treatment showed no significant differences in the mean increases in velocity of circumferential fiber shortening or ejection fraction. This finding suggests that digoxin exerts as potent an inotropic effect on a long-term basis (for at least 4 weeks) as it does acutely (Fig. 6).

Discussion

Previous studies on effect of digitalis on left ventricular performance: It is now well accepted that digitalis causes acute increases in myocardial contractility, even in the nonfailing heart, although cardiac output does not increase.[1,2,16] However, the effect of long-term digoxin administration on left ventricular performance is less clear, and relatively few studies have been done in man. One difficulty has been the limitations on the use of invasive methods to evaluate cardiac performance on a long-term basis. Noninvasive tests tend to be limited by their lack of sensitivity to small changes in left ventricular performance or by restriction of the portion of left ventricular wall available for examination. A double-blind study using physical examination and ballistocardiography demonstrated no beneficial effect of digitoxin in 11 elderly women with compensated atherosclerotic cardiovascular disease.[5] Assessment of clinical symptoms in such patients may be insensitive to small changes in cardiac function and may be influenced by factors unrelated to digitalis ingestion. In two other studies,[7,8] an abbreviation of systolic time intervals was demonstrated after 14 days of treatment with oral digoxin, whereas in a third study[9] no long-term effect on these intervals was demonstrated.

Although there is no clear explanation for the variability of these results, in one report[9] some patients were studied within 2 weeks of aortic valve replacement, whereas in a second study, 10 of 21 patients were convalescing from acute myocardial infarction.[8] In both situations, progressive alterations in cardiac performance may obscure the effect of digitalis. A favorable



* $p < 0.05$

† SDC (ng/ml): 1.2 ± 0.1 to 1.4 ± 0.1

FIGURE 5. Mean group response of velocity of circumferential fiber shortening (VCF) (**upper**) and ejection fraction (**lower panel**) for each week of oral digoxin treatment, normalized relative to initial control period. Data from four to nine cardiac cycles per week per patient were averaged each week and during the 3 week control period and 2 week recovery period. NS = not statistically significant; p = probability; SDC = serum digoxin concentration.

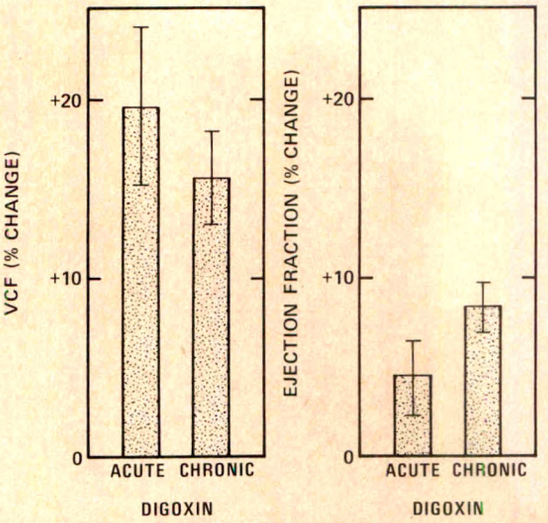


FIGURE 6. Comparison of mean group percent increase velocity of circumferential fiber shortening (VCF) (**left**) and ejection fraction (**right**) after acute intravenous digitalization (four to nine cardiac cycles per patient) and 4 weeks of oral digoxin treatment (mean data from four to nine cardiac cycles per week per patient). No significant difference between the short- and mean long-term effects was observed.

effect on ventricular performance, as assessed with videotracking, was recently demonstrated after 2 weeks of therapy with oral digoxin in patients with previous myocardial infarction.[10] Videotracking measures epicardial movement, which is more damped than endocardial or mid wall motion. The image analyzed is limited to ventricular free wall movement and may not reflect total left ventricular dynamics. Similarly, echocardiographic studies have shown inotropic effects of digoxin after a 2 week dosing period in patients with normal left ventricular function[11] who have no segmental wall motion abnormalities.

In a recent study that assessed angiographically the acute effects of intravenous ouabain, De Mots et al.[17] noted a decrease in end-diastolic volume and more prominent increases in ejection fraction and contractility than those noted in our study. This difference may in part reflect their finding of a significant reduction in mean arterial blood pressure, which is opposite to the usual blood pressure response to digitalis. This decrease in blood pressure may reflect the use of angiographic contrast medium in these studies.

Enhanced ventricular performance after acute and long-term digoxin therapy: Our results confirm prior observations that intravenous digoxin acutely augments ventricular function, as evidenced by increases in ejection fraction and velocity of circumferential fiber shortening.[1,2] We evaluated the effect of digoxin over a 4 week interval, with continuous adjustment of the digoxin dose according to weekly blood levels to maintain serum digoxin concentrations in the therapeutic range. Increased velocity of circumferential fiber shortening and ejection fraction were observed during each of the 4 weeks of drug therapy, and did not diminish with prolonged treatment. Withdrawal of digoxin resulted in the return of these variables to their predrug control levels. The increase in velocity of circumferential fiber shortening and ejection fraction induced with long-term oral digoxin administration was similar to the increases noted after rapid intravenous digitalization. These data suggest that the potential clinical benefit of drug treatment persists undiminished for at least 4 weeks.

Factors involved in enhanced ventricular performance: Because ventricular performance is modulated not only by myocardial contractility but also by preload, afterload, heart rate and autonomic tone, these factors must be examined before one can conclude that digitalis administration alone was responsible for the enhanced cardiac performance demonstrated in our short- and long-term studies. Acutely, digoxin administration resulted in an increase in mean systolic blood pressure (afterload) of 14 mm Hg, a decrease in mean heart rate of 7 beats/min and no change in mean end-diastolic volume (preload). With long-term digoxin administration, no sustained change in systolic blood pressure or end-diastolic volume was observed, and mean heart rate decreased by 7 beats/min. Therefore, augmentation of ventricular performance cannot be

ascribed to increased preload. Velocity of circumferential fiber shortening has been shown to be relatively insensitive to changes in preload, but is greatly affected by changes in afterload.[16,18] The small increases in mean systolic blood pressure that we observed in both short- and long-term studies would tend to decrease velocity of circumferential fiber shortening and ejection fraction, and minimize any enhancement of performance that occurred. Acute increases in afterload may have contributed to the small decrease in cardiac output observed after intravenous digitalization.

The decrease in heart rate produced by digoxin would also tend to decrease the velocity of circumferential fiber shortening.[16] Although no direct measure of autonomic tone was available, the reduction in mean heart rate and the unchanged mean blood pressure during the period of long-term digoxin administration argue against the occurrence of marked changes in autonomic tone that might augment ventricular contractility and performance. Indeed, acute digitalis administration has been shown to cause reflex withdrawal of sympathetic tone in autonomically intact animals.[19] Its effect on autonomic tone after long-term administration has not been studied to our knowledge. In summary, heart rate and available indexes of preload, afterload and sympathetic neural influence either showed no significant change during long-term treatment with digoxin or changed directionally so as to counteract rather than enhance the inotropic effects of digoxin.

Clinical implication: Out data clearly demonstrate a persistent improvement in left ventricular contractility and performance in response to long-term oral digoxin therapy in patients with ischemic heart disease without clinical evidence of heart failure. However, the 15 percent increase in velocity of circumferential fiber shortening and 8.5 percent increase in ejection fraction are relatively small compared with the 64 percent increase in velocity of circumferential fiber shortening and 65 percent increase in ejection fraction observed in similar subjects after infusion of isoproterenol (2 μg/min).[20] Thus, although digoxin may not be a powerful inotropic agent, our data suggest that for at least 4 weeks it exerts a sustained effect that is similar in magnitude to the effect obtained with acute intravenous administration.

Acknowledgment

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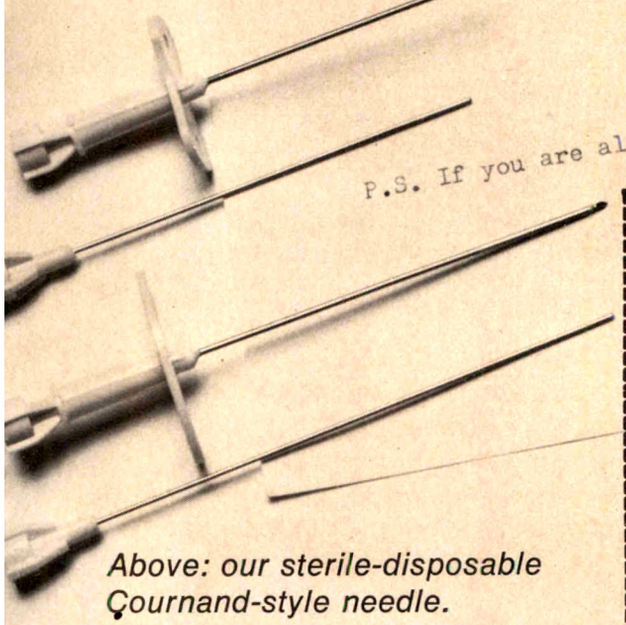
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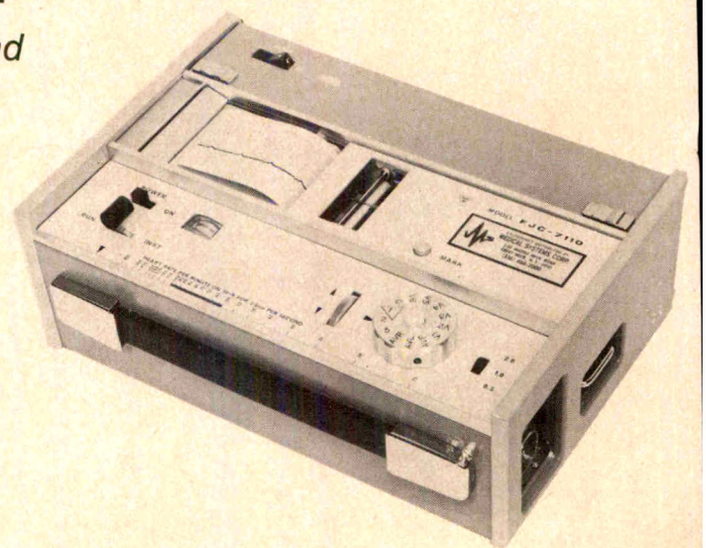
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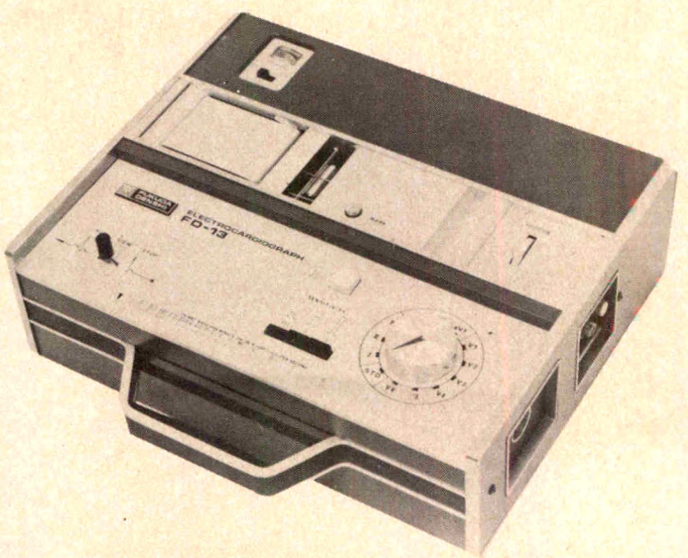
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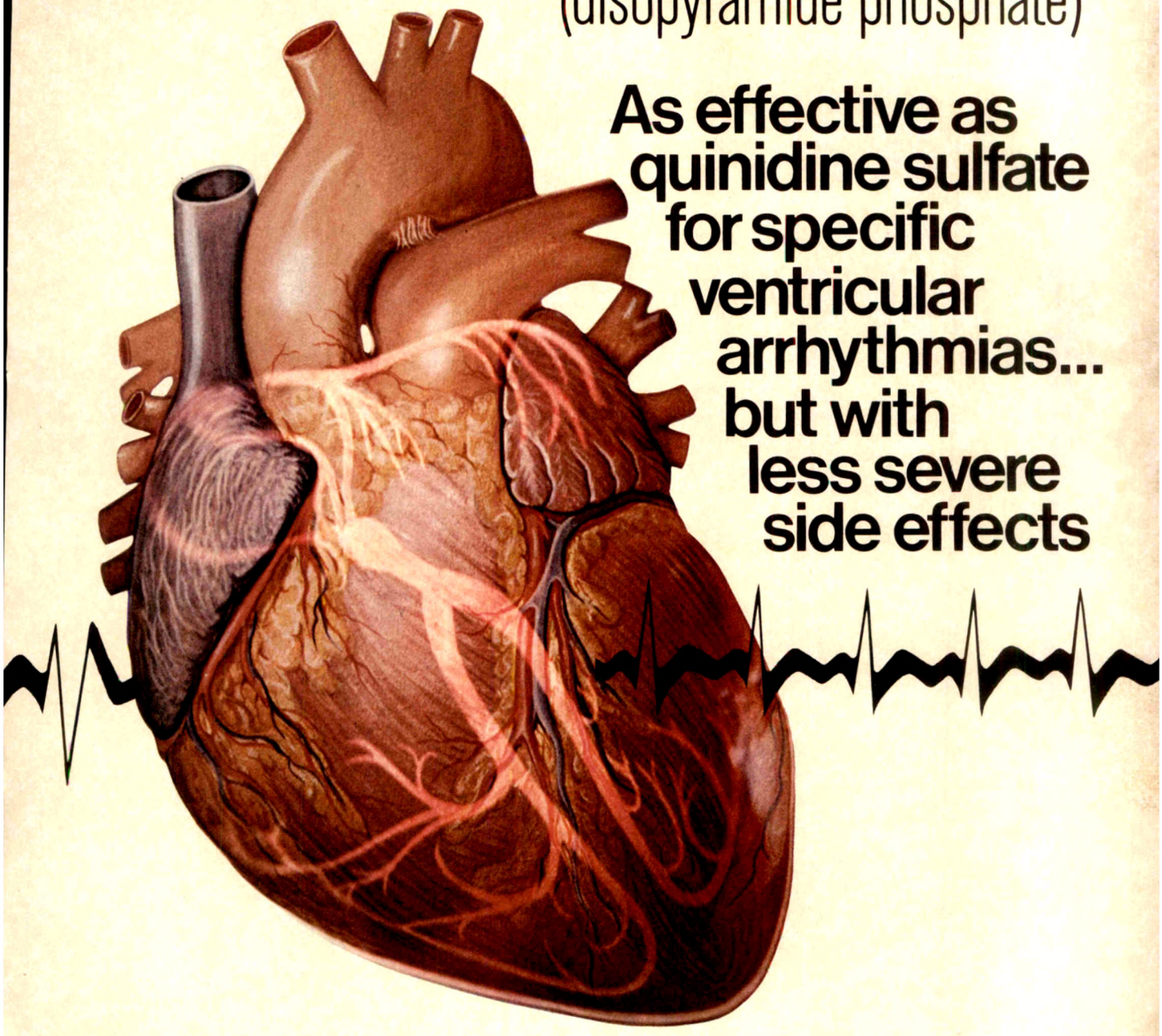
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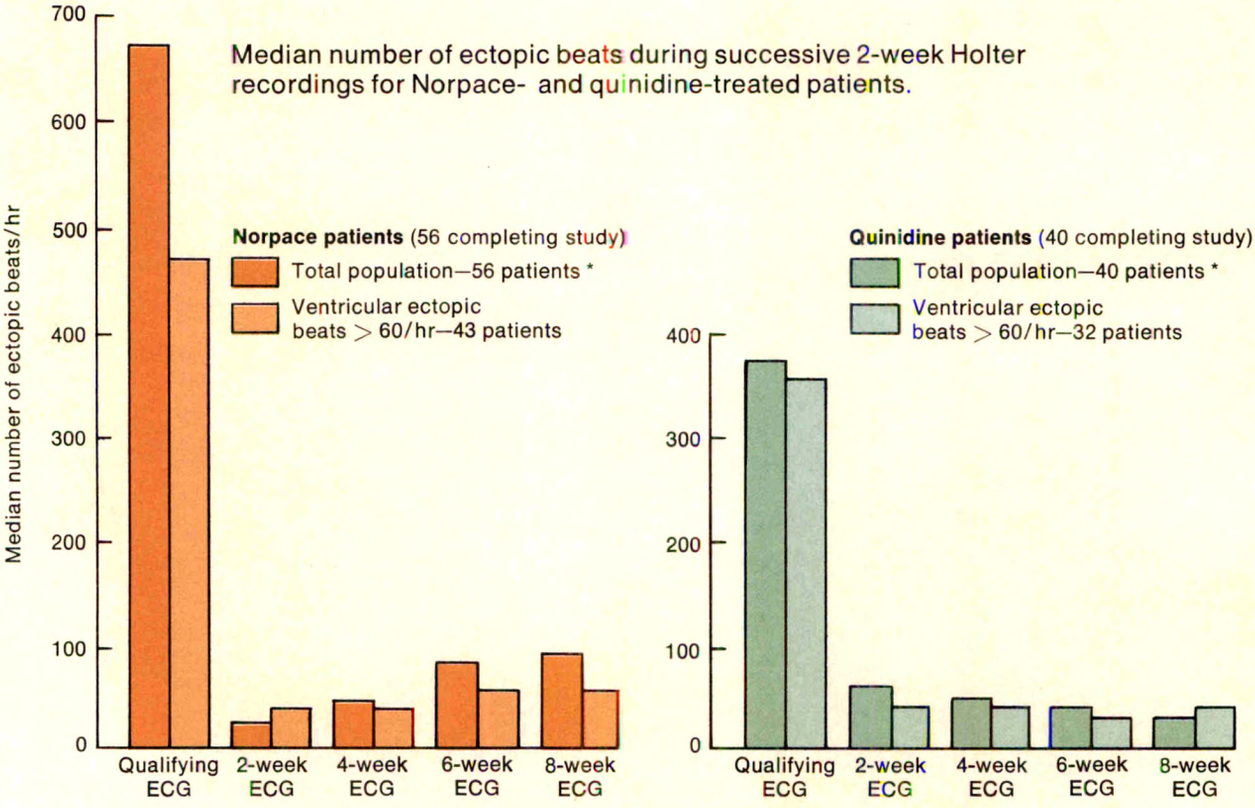
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Median number of ectopic beats during successive 2-week Holter recordings for Norpace- and quinidine-treated patients.



* Includes patients with more than 60 total (atrial and ventricular) ectopic beats per hour but who had fewer than 60 ventricular ectopic beats per hour.

There was no statistically significant difference in reduction of ectopy between the two drugs.

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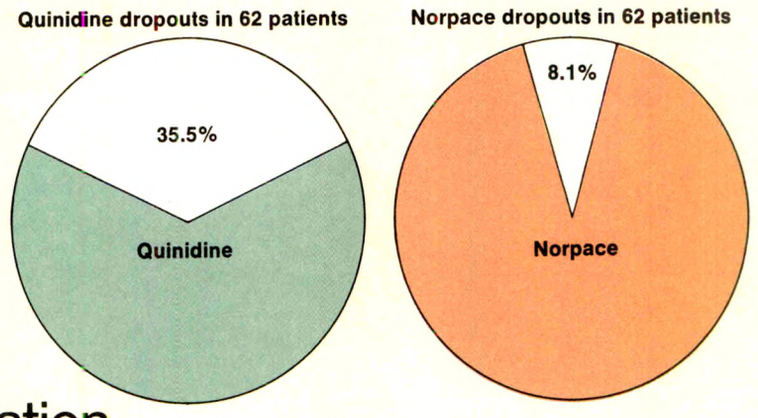
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The entire study population was analyzed for side effects. The side effects experienced by Norpace patients were usually mild and mainly anticholinergic, including: dry mouth, urinary hesitancy, constipation, blurred vision. The anticholinergic side effects were generally transient. Adverse reactions with quinidine were more serious and affected a greater number of patients. The most common symptoms were: severe diarrhea; gastrointestinal symptoms including cramps, nausea and vomiting; dizziness; fever; and rash.



Dosage and administration

Supplied as 100-mg and 150-mg capsules. Dosage should be individualized based on response and tolerance. Usual adult dosage is 400 to 800 mg per day given in divided doses four times daily.

Initial Norpace dosage

Patients 110 lb and over	150 mg q 6 h
Patients less than 110 lb	100 mg q 6 h
Patients with specific complications: Patients with *possible cardiac decompensation, cardiomyopathies, reduced left ventricular function* or *hypotension* due to these or other causes	100 mg q 6 h
Patients with moderate renal ($C_{cr} > 40$ ml/min) or hepatic insufficiency	100 mg q 6 h (200-mg loading dose optional)
Patients with severe renal insufficiency ($C_{cr} < 40$ ml/min)	100 mg given approximately every half-life (T½) (200-mg loading dose optional)
C_{cr} = 40–15 ml/min	q 10 h
C_{cr} = 15– 5 ml/min	q 20 h
C_{cr} = 5– 1 ml/min	q 30 h
In patients *without the complications* specified above in whom rapid control of arrhythmias is essential, therapy may be initiated with a loading dose of 300 mg (200 mg for patients under 110 lb).	

For complete Norpace dosage recommendations, please see full prescribing information, a brief summary of which appears on the next page.

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(disopyramide phosphate)



as effective as quinidine sulfate for specific ventricular arrhythmias...with less severe side effects

Before prescribing Norpace (disopyramide phosphate), please consult current complete prescribing information, a summary of which follows:

Indications: Norpace is indicated for suppression and prevention of recurrence of the following cardiac arrhythmias when they occur singly or in combination: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion).

Norpace is equally effective in treating the above arrhythmias in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease. Oral Norpace has not been adequately studied in patients with acute myocardial infarction or in patients with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established.

Contraindications: Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug.

Warnings: Severe hypotension has been observed primarily in patients with primary cardiomyopathy or inadequately compensated congestive heart failure. If hypotension develops Norpace should be discontinued promptly unless hypotension is due to the arrhythmia.

Norpace should not be used in the presence of poorly compensated or uncompensated congestive heart failure unless it is exacerbated by or caused by an arrhythmia and proper treatment including optimal digitalization has been accomplished. In some patients with marginally compensated heart failure, Norpace may worsen cardiac decompensation. In these patients, progressing congestive heart failure should generally be treated with cardiac glycosides and diuretics and the course of treatment closely followed. Norpace dosage should be reduced or discontinued if adequate control of congestive failure is not attained.

If first-degree heart block develops, the dosage of Norpace should be reduced. If the block persists, continuation of Norpace must depend upon an assessment of the benefit versus the risk. Development of second- or third-degree AV block or uni-, bi- or trifascicular block requires discontinuation of Norpace, unless the ventricular rate is adequately controlled by a pacemaker.

Because of its anticholinergic properties, Norpace should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken.

Precautions: If significant widening (greater than 25%) of the QRS complex occurs, Norpace should be discontinued. If Q-T prolongation greater than 25% occurs and if ectopy continues, monitor closely and consider discontinuing Norpace.

Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits.

The effect of Norpace is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block.

Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of Norpace (disopyramide phosphate).

Norpace should be administered cautiously to patients who are receiving or who have recently received other antiarrhythmic drugs. Excessive widening of the QRS complex and/or prolongation of the Q-T interval may occur in such instances.

Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage.

Antiarrhythmic drugs may be ineffective in patients with hypokalemia. Therefore, any potassium deficit should be corrected before instituting Norpace therapy.

Use in Pregnancy and Lactation: Safe use in pregnancy has not been established. Norpace has been reported to stimulate contractions of the pregnant uterus. The use of Norpace in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus.

It is not known whether disopyramide is excreted in human milk. However, studies in rats have shown that the concentration of disopyramide and its metabolites is up to three times greater in milk than in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted.

Labor and Delivery: The effects of Norpace on the fetus during delivery or on the course of labor and delivery are unknown.

Pediatrics: The safety and effectiveness of Norpace in children have not been established.

Adverse Reactions: *Anticholinergic:* dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention. *Genitourinary:* urinary frequency and urgency. *Gastrointestinal:* nausea, pain/bloating/gas, anorexia, diarrhea, vomiting. *General:* nervousness, dizziness, general fatigue/muscle weakness, headache, malaise. *Cardiovascular:* hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain. *Dermatologic:* generalized rash/dermatoses. The following have occurred, but a causal relationship is uncertain: impotence, depression, insomnia, hypoglycemia, dysuria. Acute psychosis and cholestatic jaundice, both reversible, have been reported.

Dosage and Administration: Dosage must be individualized for each patient on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg per day given in divided doses four times daily. The recommended dosage schedule for most adults is 150 mg every six hours. For patients weighing less than 110 pounds (50 kg) the recommended dosage is 100 mg every six hours.

If rapid control of arrhythmia is essential, an initial loading dose of 300 mg of Norpace (200 mg for patients weighing less than 110 pounds) is recommended. For patients with cardiomyopathy or possible cardiac decompensation, a loading dose should not be given and the initial dose limited to 100 mg every six hours, with subsequent dosage adjustments made gradually under close monitoring.

See current complete prescribing information for dosage recommendations.

How Supplied: Capsules containing 100 mg or 150 mg of disopyramide base. Available in bottles of 100 capsules.

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How Dynavit functions: A pulse sensor provides heart rate input. Patients enter their age, weight and sex on the push-button console. Individual target heart rate—and a light warm-up workload are digitally displayed. Target heart rate can be decreased (or increased) in one beat increments to any prescribed level; workload in 10 watt increments from 50 to 300. Visual signals help the patient work within the prescribed target range.

In addition, pressing appropriate buttons instantly displays actual heart rate, elapsed time, calories expended and exercise units.

After each 10 minutes of exercise, the computer calculates a numerical index of functional capacity. This index is compatible with the Cardiorespiratory Fitness Classification Tables of the American Heart Association.

Learn how computerized Dynavit exercise can serve as an adjunct in the prevention and rehabilitation of heart disease through improved compliance with a regimen of exercise. For a demonstration and further data, phone toll free 800-253-0856; in Michigan call collect 616-962-5473. Or use the coupon below. Dynavit of America, Inc., 5701 W. Dickman Road, Battle Creek, Michigan 49015.

KEEP FIT ON A **dynavit®**

Dynavit of America, Inc.,
P.O. Box 1280, Dept. AJC—1,
Battle Creek, Michigan 49016

☐ I would like a demonstration of the DYNAVIT ergometer.
☐ I would like more information on the DYNAVIT ergometer.

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City_____ State_____

Zip_____ Phone_____

Please check appropriate box:
☐ Cardiologist ☐ Administrator ☐ Internist
☐ Physical Therapist ☐ Cardiopulmonary Technician
☐ Other_____

8205

Change of pace...

From CPI, the versatile new MICROLITH-P, for precision programming of both pulse rate and width at the touch of a button.

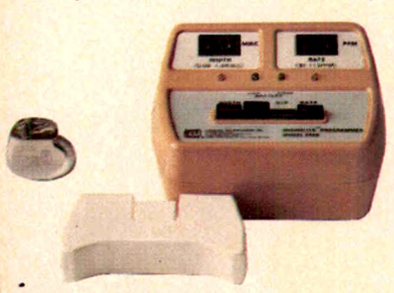
People change. And because a pacemaker must become an integral part of a human being, CPI® designed the new MICROLITH®-P, the only non-invasive programming system that makes precise adjustment of both pulse rate and width a simple pushbutton operation. With the quartz-crystal-controlled MICROLITH-P, you can adjust rate from 30 to 119 ppm in single pulse increments... width from 0.1 to 1.9 ms in 0.1 ms increments (.05 ms can also be programmed). It's all done with a compact, digital programmer that's easier to use than a pocket calculator. It takes less than 2.5 seconds. And a simple EKG reading lets you know immediately that the program's been accepted. Fast, flexible, accurate pace-changing at your office or the hospital.

Even the shape of the MICROLITH-P is new. Semi-elliptical. With more rounded surface on the external side to look and feel more natural... to reduce risk of pocket complications. With more flat surface on the internal side to minimize migration and tissue erosion. Small. Thin. Lightweight. A shape that's a natural to simplify implantation and assure patient comfort.

And there's more • Superior moisture resistance thanks to a special new parylene coating used only by CPI for encapsulating internal circuitry • Time-tested lithium power source and hybrid C-MOS circuitry • Predictable 2-step elective replacement time (ERT) indicator • Excellent electromagnetic interference (EMI) rejection • Runaway protection • Multiple hermetic sealing • X-Ray identification • Demand mode with choice of unipolar and bipolar configurations • Compatibility with most commonly used leads • A limited warranty for up to 6 years*

MICROLITH-P... another advanced CPI pacing system backed by 5 years of successful experience with lithium pulse generators that continue to set industry standards for reliability. Find out more today by writing or calling CPI toll free, 800-328-9588.

**Warranty statement available upon request*

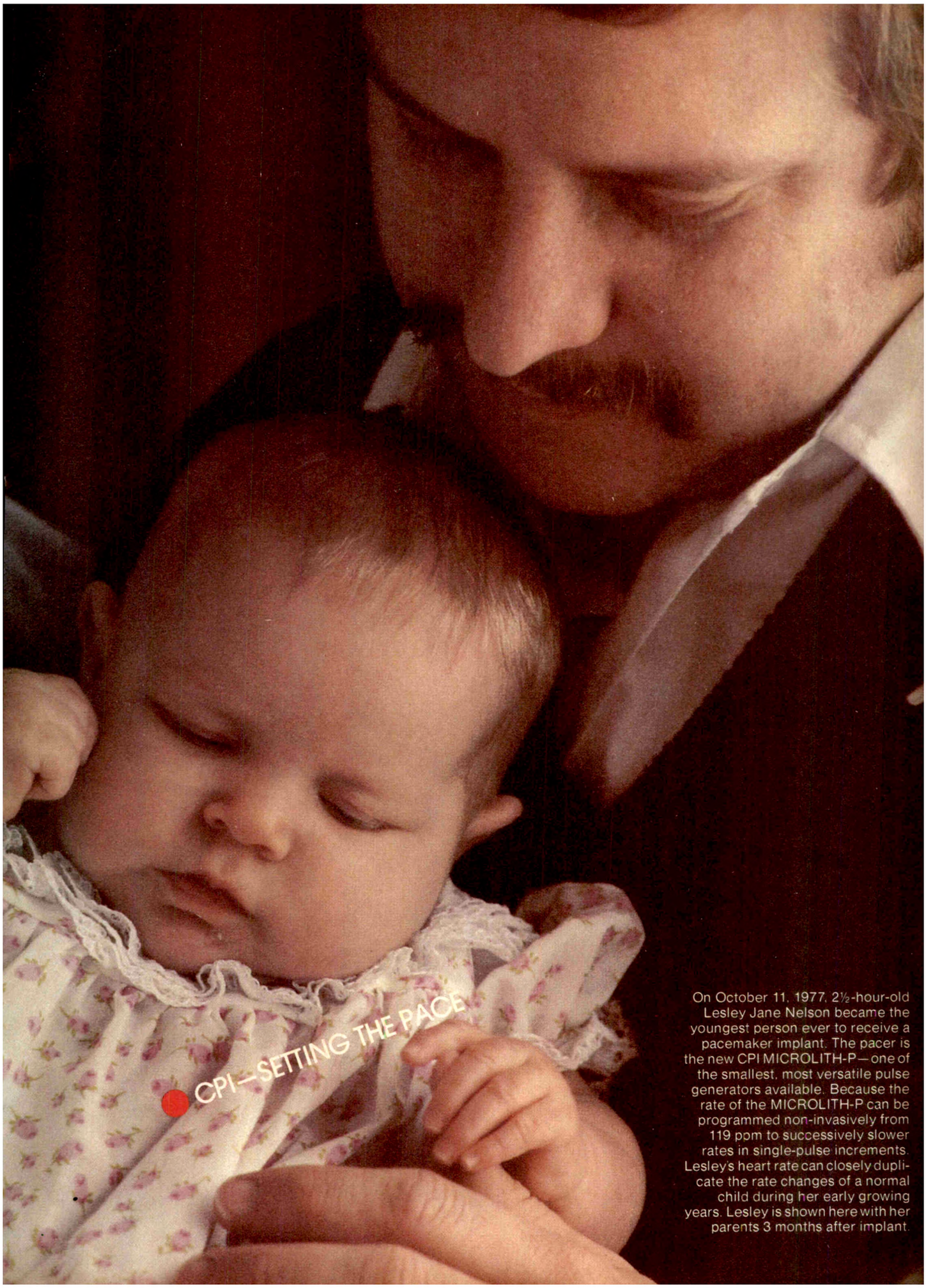


CPI®

Cardiac Pacemakers, Inc.
4100 North Hamline Avenue
P.O. Box 43079
St. Paul, Minnesota 55164, U.S.A.
Telephone: (612) 631-3000
Cable: Cardiapace, St. Paul
Telex: 29-7049

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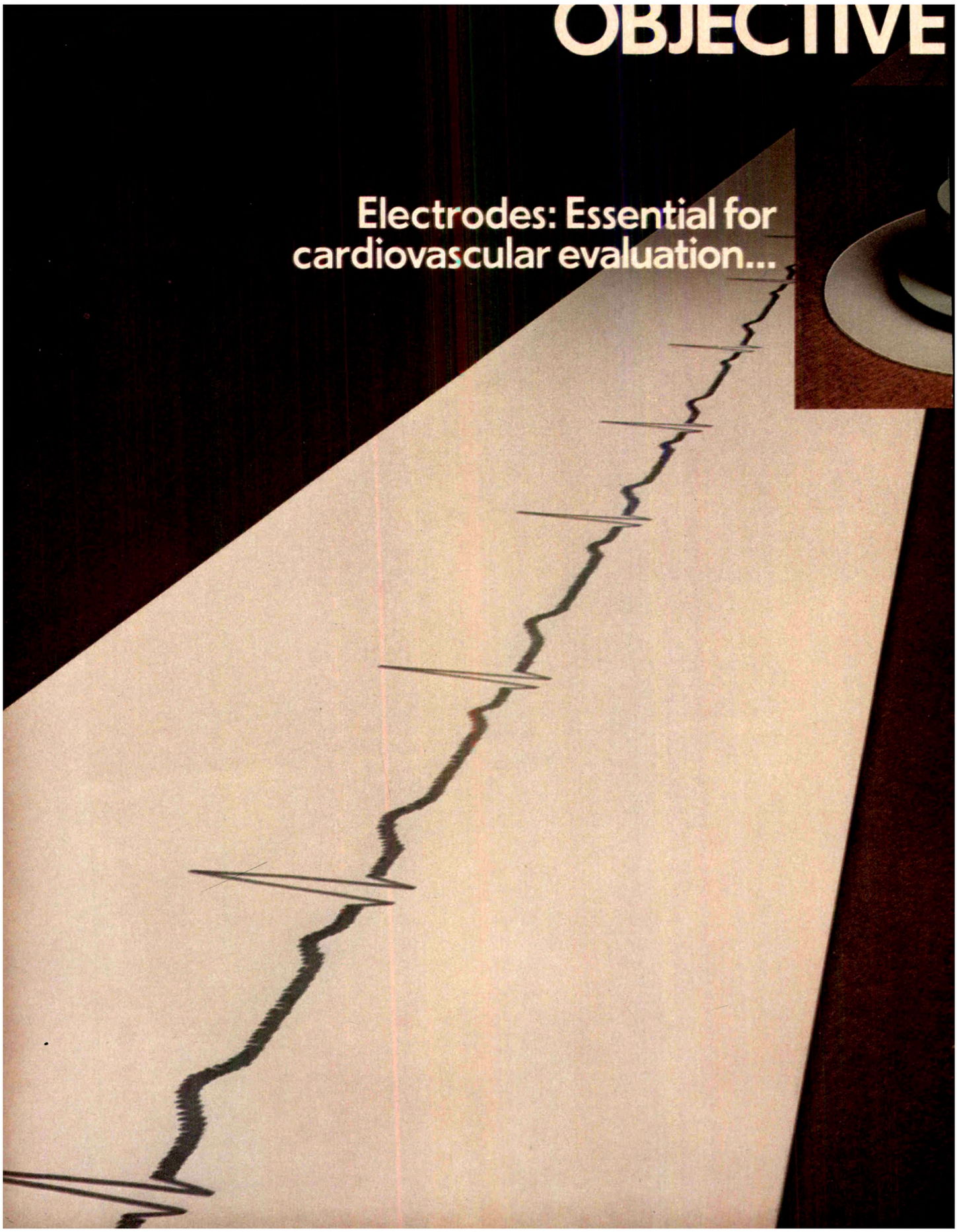




On October 11, 1977, 2½-hour-old Lesley Jane Nelson became the youngest person ever to receive a pacemaker implant. The pacer is the new CPI MICROLITH-P—one of the smallest, most versatile pulse generators available. Because the rate of the MICROLITH-P can be programmed non-invasively from 119 ppm to successively slower rates in single-pulse increments. Lesley's heart rate can closely duplicate the rate changes of a normal child during her early growing years. Lesley is shown here with her parents 3 months after implant.

OBJECTIVE

Electrodes: Essential for cardiovascular evaluation...



ROCHE

EVALUATION



just as essential for objective hypnotic evaluation

Just as the electrocardiogram is an essential part of every cardiovascular examination, sleep laboratory polysomnography (EEG, EMG, EOG) is an essential part of every objective examination of hypnotic efficacy. In fact, data derived from the all-night sleep laboratory are the basis of a scientific approach to the evaluation and alleviation of insomnia.

One hypnotic has undergone sleep laboratory investigation in *more* patients than any other medication for insomnia. That sleep medication is Dalmane (flurazepam HCl). In objective evaluations, Dalmane has proved more effective for more nights than any other agent for insomnia.[1-10]

DALMANE®
(flurazepam HCl) C IV
30-mg and 15-mg capsules
THE MODEL OF HYPNOTIC EFFICACY

Please see following page for a summary of product information.

DALMANE®
(flurazepam HCl) C-IV

One 30-mg capsule *h.s.*—usual adult dosage
(15 mg may suffice in some patients).
One 15-mg capsule *h.s.*—initial dosage for elderly or debilitated patients.

Before prescribing Dalmane (flurazepam HCl), please consult complete product information, a summary of which follows:
Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Usage in Pregnancy: **Several studies of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) suggest increased risk of congenital malformations during the first trimester of pregnancy. Dalmane, a benzodiazepine, has not been studied adequately to determine whether it may be associated with such an increased risk. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.
Precautions: In elderly and debilitated, limit initial dosage to 15 mg to preclude oversedation, dizziness and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.
Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase.
Dosage: Individualize for maximum beneficial effect.
Adults: 30 mg usual dosage; 15 mg may suffice in some patients.
Elderly or debilitated patients: 15 mg initially until response is determined.
Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

REFERENCES: 1. Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ. 2. Dement WC: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ. 3. Dement WC, *et al:* Long-term effectiveness of flurazepam 30 mg *h.s.* on chronic insomniacs. Presented at the 15th annual meeting of the Association for Psychophysiological Study of Sleep, Edinburgh Scotland, Jun 30-Jul 4, 1975. 4. Frost JD Jr: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ. 5. Kales A, *et al: Arch Gen Psychiatry 23*:226-232, Sep 1970. 6. Kales A, *et al: Clin Pharmacol Ther 18*:356-363, Sep 1975. 7. Kales A, *et al: J Clin Pharmacol 17* (4): 207-213, Apr 1977. 8. Kales J, *et al: Clin Pharmacol Ther 12*:691-697, Jul-Aug 1971. 9. Karacan I, Williams RL, Smith JR: The sleep laboratory in the investigation of sleep and sleep disturbances. Scientific exhibit at the 124th annual meeting of the American Psychiatric Association, Washington DC, May 3-7, 1971. 10. Vogel GW: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ

ROCHE
ROCHE PRODUCTS INC.
Manati, Puerto Rico 00701

Peritrate® SA
Sustained Action
(pentaerythritol tetranitrate) **80 mg**
Peritrate®
(pentaerythritol tetranitrate) **40 mg**
Peritrate®
(pentaerythritol tetranitrate) **20 mg**
Peritrate®
(pentaerythritol tetranitrate) **10 mg**

CAUTION: Federal law prohibits dispensing without prescription.
Description: Each tablet of Peritrate SA Sustained Action contains: pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Each tablet of Peritrate 40 mg contains pentaerythritol tetranitrate 40 mg. Each tablet of Peritrate 20 mg contains pentaerythritol tetranitrate 20 mg. Each tablet of Peritrate 10 mg contains pentaerythritol tetranitrate 10 mg. Peritrate (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg and Peritrate (pentaerythritol tetranitrate) are contraindicated in patients who have a history of sensitivity to the drug.
Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.
This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.
Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.
Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe, persistent headaches may occur.
In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:
(a) Cutaneous vasodilatation with flushing.
(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.
(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.
Dosage: Peritrate (pentaerythritol tetranitrate) may be administered in individualized doses up to 160 mg a day. Dosage can be initiated at one 10 mg or 20 mg tablet q.i.d. and titrated upward to 40 mg (two 20 mg tablets or one 40 mg tablet) q.i.d. one-half hour before or one hour after meals and at bedtime. Alternatively, Peritrate Sustained Action 80 mg can be administered on a convenient b.i.d. dosage schedule.
Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg—double-layer, biconvex, dark green/light green tablets in bottles of 100 (N 0047-0004-51) and 1000 (N 0047-0004-60). Also unit dose, package of 10 x 10 strips (N 0047-0004-11).
Peritrate (pentaerythritol tetranitrate) 40 mg—pink scored tablets in bottles of 100 (N 0047-0008-51).
Peritrate (pentaerythritol tetranitrate) 20 mg—light green, scored tablets in bottles of 100 (N 0047-0001-51) and 1000 (N 0047-0001-60). Also unit dose, package of 10 x 10 strips (N 0047-0001-11).
Peritrate (pentaerythritol tetranitrate) 10 mg—light green, unscored tablets in bottles of 100 (N 0047-0007-51) and 1000 (N 0047-0007-60).
STORE BETWEEN 59° and 86° F (15° and 30° C).
Animal Pharmacology: In a series of carefully designed studies in pigs, Peritrate (pentaerythritol tetranitrate) was administered for 48 hours before an artifically induced occlusion of a major coronary artery and for seven days thereafter. The pigs were sacrificed at various intervals for periods up to six weeks. The result showed a significantly larger number of survivors in the drug-treated group. Damage to myocardial tissue in the drug-treated survivors was less extensive than in the untreated group. Studies in dogs subjected to oligemic shock through progressive bleeding have demonstrated that Peritrate (pentaerythritol tetranitrate) is vasoactive at the post-arteriolar level, producing increased blood flow and better tissue perfusion. These animal experiments cannot be translated to the drug's actions in humans.
Full information is available on request.

W|C
Warner/Chilcott
Division,
Warner-Lambert Company
Morris Plains, N.J. 07950



Prescribe Maximum Peritrate Dosage Simply and Conveniently

Peritrate® 40mg Tablets q.i.d.

(pentaerythritol tetranitrate)

40 mg q.i.d.

40 mg q.i.d.
40 mg q.i.d.
40 mg q.i.d.
40 mg q.i.d.
40 mg q.i.d.
40 mg q.i.d.

In many angina* patients, response to Peritrate is optimum when dosage is titrated to its maximum

The simple aim of Peritrate prophylaxis* is to maintain adequate nitrate levels in the body so that fewer "breakthrough" angina attacks occur. To achieve this goal, many patients require maximum dosage.

Peritrate 40 mg tablets q.i.d. or Peritrate® SA Sustained Action 80 mg b.i.d. Whichever form of Peritrate you choose, be sure you use it optimally. You can expect side effects to be few.

*This drug has been evaluated as possibly effective for this indication.
See brief summary.

PE GP-74

160 mg/day



The Tunturi ergometer is built to measure precise amounts of work with a variable watt load range of 25 to 300w at 50 rpm. The Tunturi is quiet, affordable and portable, providing exercise your patients can live with.

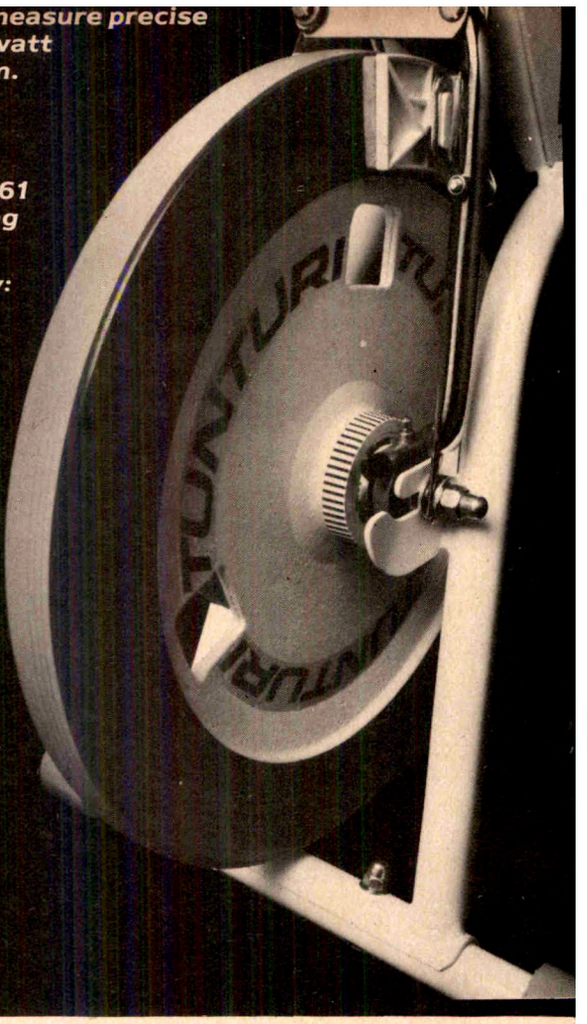
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Tunturi Ergometer:

At home rehabilitation you can prescribe from your office.



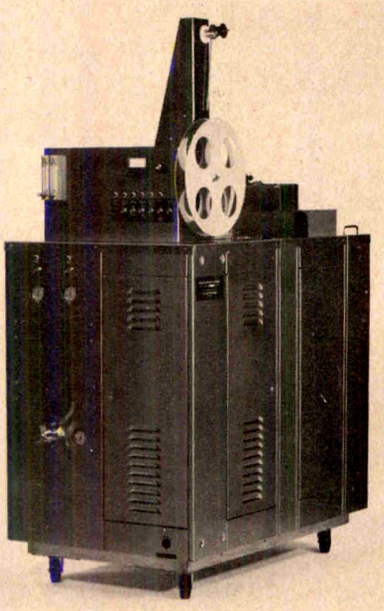
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CINE FILM PROCESSORS

Cardiac Emergency...

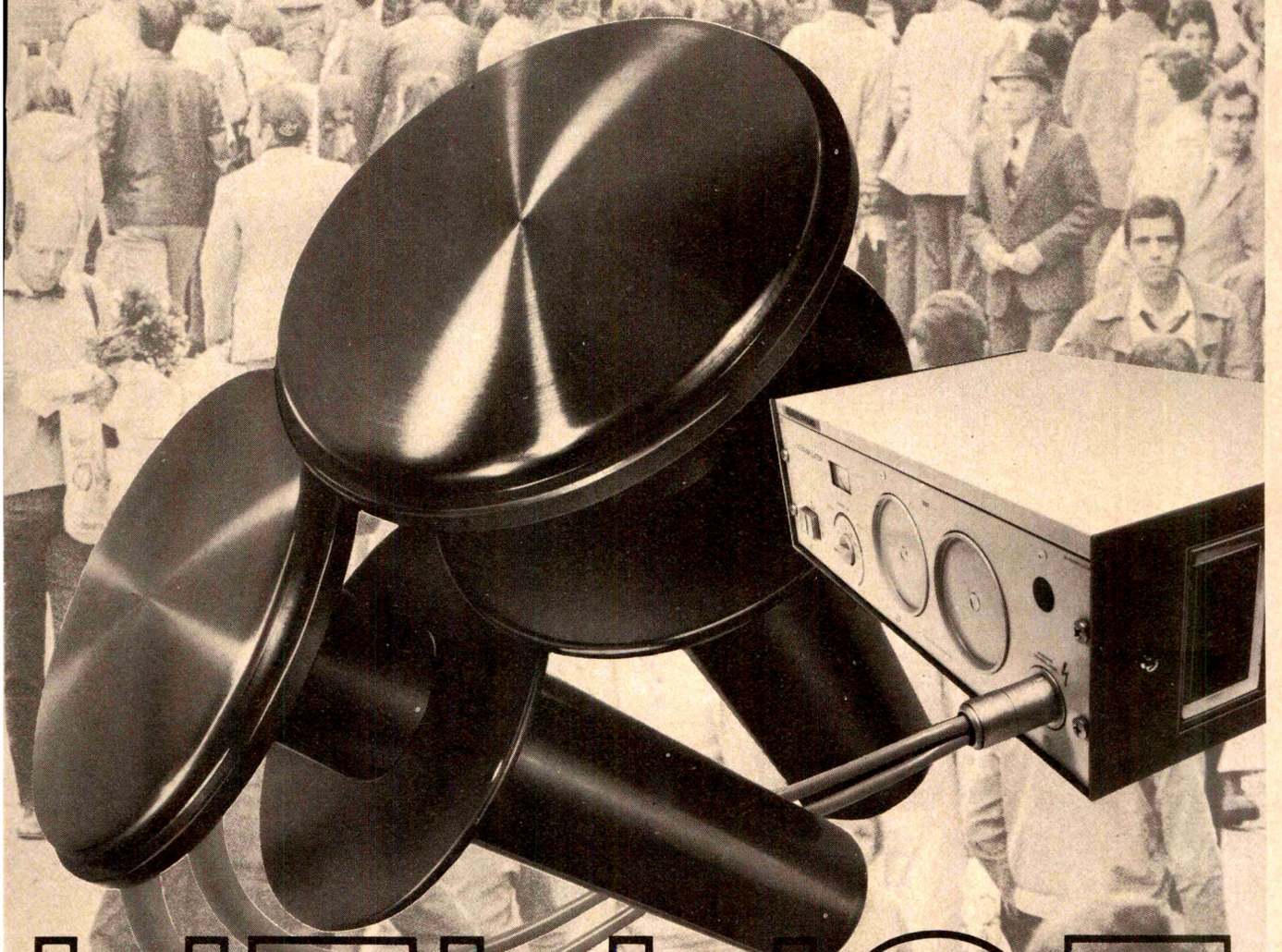
In recent times, there has been an alarming increase in the occurrence of cardiovascular diseases. However, electrotherapy has played an important part in lowering the mortality rate in critical cardiac situations. SERVOCARD from HELLIGE – a range of mobile and stationary emergency equipment for:

- Defibrillation
- Emergency pacing with the defibrillator electrodes
- Transvenous and esophageal pacing
- Rapid ECG diagnosis with battery-powered cardioscope.

The SERVOCARD program is complemented by the HLR 850 for:

- Continuous external cardiac massage and automatic oxygen ventilation from the site of the accident to the hospital.

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KayCiel®
(potassium chloride)
vs. Diet



ORANGE FLAVORED

KayCiel® Elixir		KayCiel® Powder	
Each 15 ml (20 mEq of potassium chloride) contains:		Each *Solodose*® packet (20 mEq of potassium chloride) contains:	
Calories	17	Calories	0
Sodium	0 mg	Sodium	0 mg

CONTRAINDICATIONS: Impaired renal function, untreated Addison's Disease, dehydration, heat cramps and hyperkalemia.
WARNING: Do not use excessively.
PRECAUTIONS: Administer with caution and adjust to the requirements of the individual patient. The patient should be checked frequently and periodic ECG and/or plasma potassium levels made. Use with caution in patients with cardiac disease. In hypokalemic states, attention should be directed toward the correction of the frequently associated hypochloremic alkalosis.
Patients should be cautioned to adhere to dilution instructions.
ADVERSE REACTIONS: Potassium intoxication indicated by listlessness, mental confusion, paresthesia of the extremities, weakness of the legs, flaccid paralysis, fall in blood pressure, cardiac depression, arrhythmias, arrest and heart block. Vomiting, nausea, abdominal discomfort and diarrhea may occur.
OVERDOSAGE: In case of excessive use resulting in hyperkalemia or potassium intoxication, discontinue potassium chloride administration or take other steps to lower serum levels if indicated.

Cooper Compliance Tip

Help assure that your older patients take medications properly by printing your instructions in large letters. You might also send a copy of the instructions to the patient's spouse. Please forward your compliance tip to Cooper Laboratories, 300 Fairfield Road, Wayne, N.J. 07470, Att: W.F. Cronin.

Cooper Laboratories, Wayne, New Jersey 07470 143-48

PRONESTYL® TABLETS (Procainamide Hydrochloride Tablets)
PRONESTYL® CAPSULES (Procainamide Hydrochloride Capsules U.S.P.)

The prolonged administration of procainamide often leads to the development of a positive anti-nuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate considerations of alternative anti-arrhythmic therapy.

DESCRIPTION: Pronestyl (Procainamide Hydrochloride) is the amide analogue of procaine hydrochloride and is available for oral administration as capsules and veneer-coated tablets providing 250 mg., 375 mg., and 500 mg. procainamide hydrochloride.
CONTRAINDICATIONS: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; bear in mind cross sensitivity to procaine and related drugs. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of second degree and third degree A-V block unless an electrical pacemaker is operative.
ADMINISTRATION: Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.
PRECAUTIONS: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous if myocardial damage exists.

The dislodgment of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in second degree and third degree A-V block, bundle branch block, or severe digitalis intoxication.

Bear in mind when treating ventricular arrhythmias in patients with severe organic heart disease and ventricular tachycardia that complete heart block, which may be difficult to diagnose, may be present. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; in event of rising titer (anti-nuclear antibody) or clinical symptoms of LE, assess the benefit/risk ratio related to continued procainamide therapy (see boxed Warning). Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.
ADVERSE REACTIONS: Hypotension is rare with oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reported (see Precautions). Reactions consisting of fever and chills have been reported, including a case with nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy; and the patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever or any symptoms of upper respiratory tract infection. If any of these symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, and hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported.

The package insert should be read carefully to become familiar with the recommended dosage for the indicated conditions and for full prescribing information.
HOW SUPPLIED: Pronestyl Tablets (Procainamide Hydrochloride Tablets) and Pronestyl Capsules (Procainamide Hydrochloride Capsules U.S.P.) providing 250 mg., 375 mg., and 500 mg. are available in bottles of 100 and Unimatic® single-dose packaging in cartons of 100. The 250 mg. and 500 mg. tablets and capsules are also available in bottles of 1000.

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tried and true

in the treatment of life-threatening arrhythmias

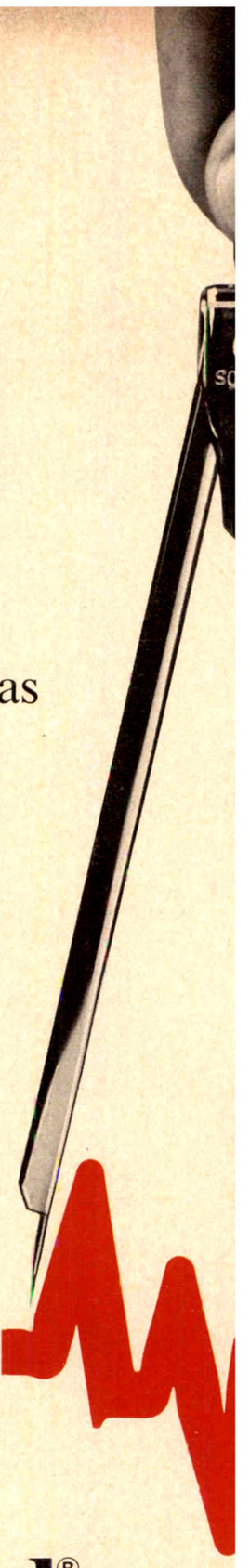
Documented effectiveness in ventricular arrhythmias; indicated for certain atrial arrhythmias as well.

Backed by 26 years of clinical experience; over 15,000,000 prescriptions written!

Extensively used and studied in post-MI patients.

Compatibility with other cardiovascular drugs researched.

Three oral strengths (250mg, 375mg, 500mg) for dosing flexibility; available in easy-to-swallow veneer coated tablets.

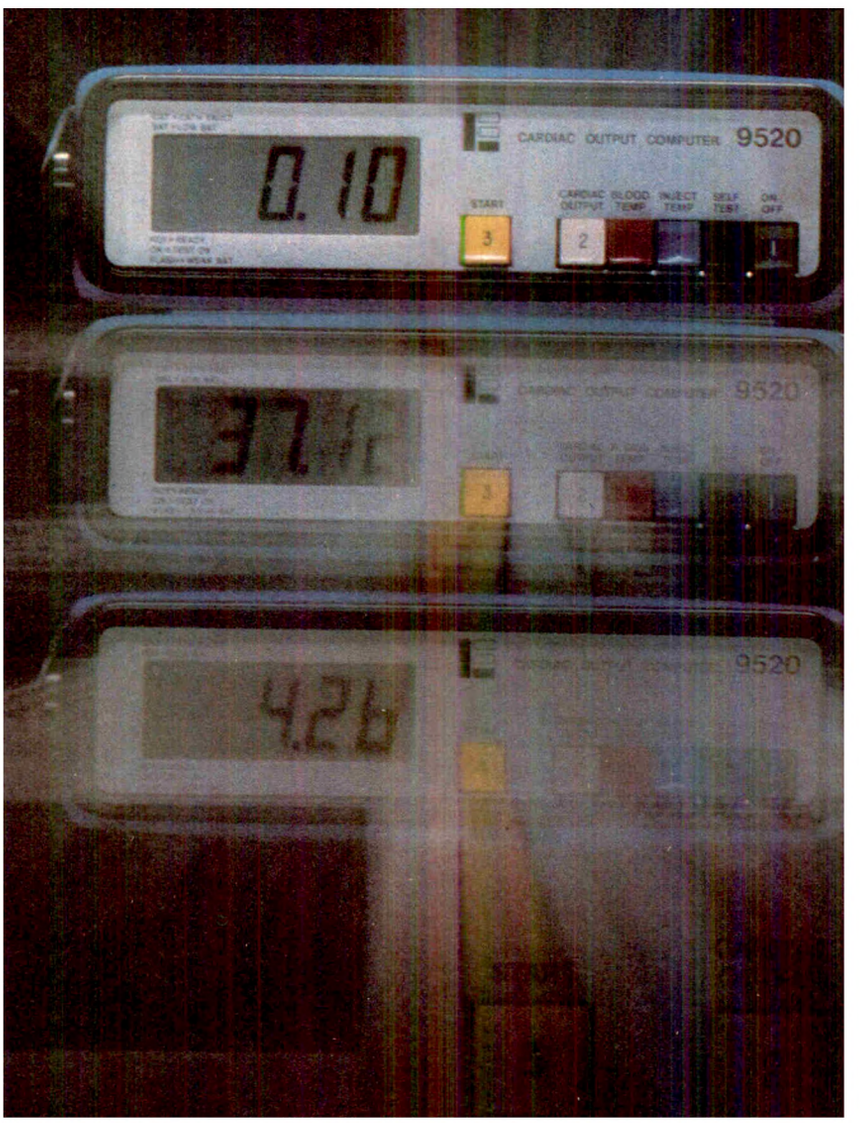


See preceding page for brief summary.

Pronestyl® Tablets

Procainamide Hydrochlor

Trustworthy antiarrhythmic


0.10
CARDIAC OUTPUT COMPUTER 9520
START
3
CARDIAC OUTPUT
2
BLOOD TEMP
INJECT TEMP
SELF TEST
ON OFF
1
9520
4.26
9520

Cardiac Output. It's as easy as 1, 2, 3.

1. Valuable in the management of critically ill patients.

- Aids in rapid assessment of patient's condition.
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2. Easy to operate.

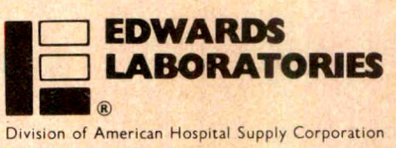
- Just press CARDIAC OUTPUT, press START and inject.
- Directly compatible with SWAN-GANZ® Thermodilution Catheters.
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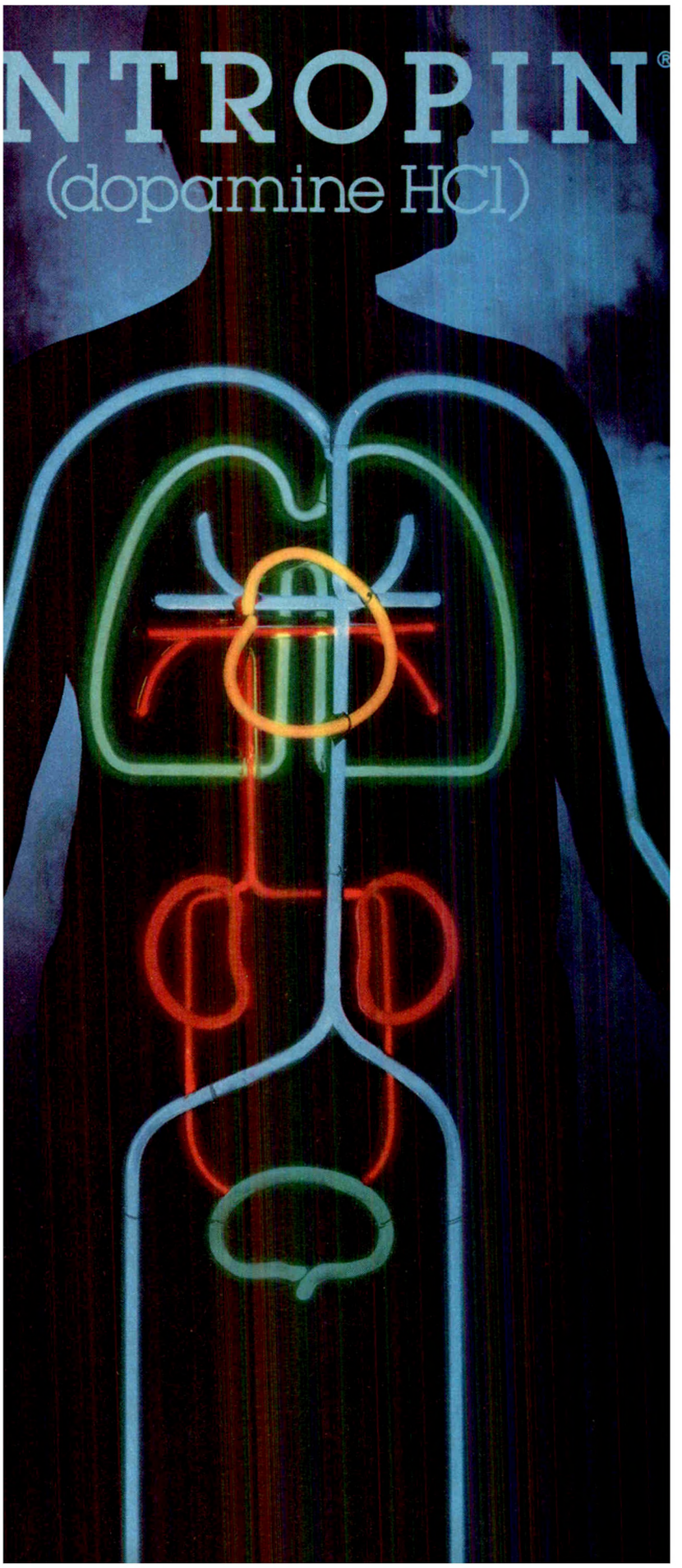
For our fact-filled technical bulletin on the EDWARDS' MODEL 9520 THERMODILUTION CARDIAC OUTPUT COMPUTER, please phone or write: Edwards Laboratories, Division of American Hospital Supply Corporation, 17221 Red Hill Avenue (Irvine), P.O. Box 11150, Santa Ana, CA 92711. 714/557-8910. Cable Address: EDSLAB. Telex: 68-5567.

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A99


NTROPIN®
(dopamine HCl)

In the shock syndrome:

Selectively redirects blood to vital organs

Increases vital organ perfusion

In the shock syndrome, perfusion pressure usually does not meet the metabolic needs of the vital organs. When volume replacement fails to reverse this process, additional therapy must be initiated to increase cardiac output and blood pressure and to increase blood flow to vital organs.

Intropin (dopamine HCl) is the only drug that both increases cardiac output and blood pressure while specifically redirecting the blood flow.

Maintains kidney function

The unique ability of Intropin to act on the "dopaminergic" receptors in the mesenteric and renal vasculature causes vasodilation in these beds and leads to increased renal blood flow, glomerular filtration rate and urine output. At low dose levels (less than 5 mcg/kg/min), when cardiac stimulation is not usually observed, these increases are independent of increased cardiac output.

In comparison, norepinephrine causes vasoconstriction in these beds, further compromising vital organ function.[1] Isoproterenol causes generalized systemic vasodilation (thereby requiring greater cardiac output to increase vital organ perfusion) and does not increase the renal fraction of the increased cardiac output.[2]

Increases cardiac output

At higher doses (above 5 mcg/kg/min), Intropin begins to increase myocardial contractility, stroke volume and cardiac output by direct positive inotropic effect while maintaining much of the unique dopaminergic effect. In certain patients such as refractory congestive failure patients, the increase in cardiac output may be seen at doses of less than 5 mcg/kg/min.

Norepinephrine, on the other hand, has a similar inotropic effect, but the expected increase in cardiac output is often diminished due to the increased systemic vascular resistance (afterload) resulting from norepinephrine's alpha adrenergic activity. Isoproterenol increases cardiac output in part through a chronotropic effect.[3] Its use results in a greater increase in myocardial oxygen consumption than does the inotropic effect of Intropin. It also results in a greater potential for arrhythmias.[3] The increased cardiac output obtained with isoproterenol is delivered to the total systemic vasculature due to general vasodilation while the selective vasodilation of Intropin directs more blood supply to the areas in need of vital perfusion.

Increases blood pressure

Intropin doses of over 20 mcg/kg/min will usually result in an alpha adrenergic (vasoconstriction) response in the peripheral vasculature. This usually raises the pressure and also redirects blood flow through the vasodilated vasculature of the renal and mesenteric beds. Thus, Intropin can increase blood pressure through an inotropic cardiac response or at doses above 20 mcg/kg/min through an additional peripheral vasculature response.

References:
1. Rosenblum, R., Am. Heart J., 87:527-530, 1974.
2. Goldberg, L.I., N.E.J. of Med., 291:707-710, 1974.
3. Harrison, D.C., Am. J. of Card., 35:656-659, 1975.

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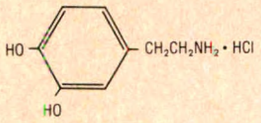
INTROPIN® (dopamine HCl)

(See last page of this advertisement for full prescribing information.)

INTROPIN® (dopamine HCl)

5 ml. AMPUL/FOR I.V. INJECTION

DESCRIPTION: INTROPIN (dopamine HCl) is 3, 4-dihydroxyphenethylamine hydrochloride, a naturally-occurring biochemical catecholamine precursor of norepinephrine. The chemical structure is:



$C_8H_{11}NO_2 \cdot HCl$ Mol. Wt. 189.65

Dopamine hydrochloride is a white, odorless crystalline powder, freely soluble in water and soluble in alcohol. It is sensitive to light, alkalis, iron salts and oxidizing agents.

Each milliliter of sterile, pyrogen-free INTROPIN Injection contains 40 mg. of dopamine hydrochloride (equivalent to 32.96 mg. of dopamine base) in Water for Injection, USP, containing 1% sodium bisulfite as a preservative.

ACTIONS: INTROPIN exerts an inotropic effect on the myocardium resulting in an increased cardiac output. INTROPIN produces less increase in myocardial oxygen consumption than isoproterenol and its use is usually not associated with a tachyarrhythmia. Clinical studies indicate that INTROPIN usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure. Total peripheral resistance at low and intermediate therapeutic doses is usually unchanged. Blood flow to peripheral vascular beds may decrease while mesenteric flow increases. INTROPIN has also been reported to dilate the renal vasculature presumptively by activation of a "dopaminergic" receptor. This action is accompanied by increases in glomerular filtration rate, renal blood flow, and sodium excretion. An increase in urinary output produced by dopamine is usually not associated with a decrease in osmolality of the urine.

INDICATIONS: INTROPIN is indicated for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Where appropriate, restoration of blood volume with a suitable plasma expander or whole blood should be instituted or completed prior to administration of INTROPIN.

Patients most likely to respond adequately to INTROPIN are those in whom physiological parameters, such as urine flow, myocardial function, and blood pressure, have not undergone profound deterioration. Multiclinic trials indicate that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and INTROPIN, the better the prognosis.

Poor Perfusion of Vital Organs – Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. Nevertheless, the physician should also observe the patient for signs of reversal of confusion or comatose condition. Loss of pallor, increase in toe temperature, and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Clinical studies have shown that when INTROPIN is administered before urine flow has diminished to levels approximately 0.3 ml./minute, prognosis is more favorable. Nevertheless, in a number of oliguric or anuric patients, administration of INTROPIN has resulted in an increase in urine flow which in some cases reached normal levels. INTROPIN may also increase urine flow in patients whose output is within normal limits and thus may be of value in reducing the degree of pre-existing fluid accumulation. It should be noted that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Concurrent administration of INTROPIN and diuretic agents may produce an additive or potentiating effect.

Low Cardiac Output – Increased cardiac output is related to INTROPIN's direct inotropic effect on the myocardium. Increased cardiac output at low or moderate doses appears to be related to a favorable prognosis. Increase in cardiac output has been associated with either static or decreased systemic vascular resistance (SVR). Static or decreased SVR associated with low or moderate increments in cardiac output is believed to be a reflection of differential effects on specific vascular beds with increased resistance in peripheral beds (e.g. femoral) and concomitant decreases in mesenteric and renal vascular beds. Redistribution of blood flow parallels these changes so that an increase in cardiac output is accompanied by an increase in mesenteric and renal blood flow. In many instances the renal fraction of the total cardiac output has been found to increase. Increase in cardiac output produced by INTROPIN is not associated with substantial decreases in systemic vascular resistance as may occur with isoproterenol.

Hypotension – Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of INTROPIN, which have little effect on SVR. At high therapeutic doses, INTROPIN's alpha adrenergic activity becomes more prominent and thus may correct hypotension due to diminished SVR. As in the case of other circulatory decompensation states, prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, it is suggested that the physician administer INTROPIN as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

CONTRAINDICATIONS: INTROPIN should not be used in patients with pheochromocytoma.

WARNINGS: INTROPIN should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

Do **NOT** add INTROPIN to any alkaline diluent solution, since the drug is inactivated in alkaline solution.

Patients who have been treated with monamine oxidase (MAO) inhibitors prior to the administration of INTROPIN will require substantially reduced dosage. Dopamine is metabolized by MAO, and inhibition of this enzyme prolongs and potentiates the effect of INTROPIN. The starting dose in such patients should be reduced to at least one-tenth (1/10) of the usual dose.

Usage in Pregnancy – Animal studies have revealed no evidence of teratogenic effects from INTROPIN. In one study, administration of INTROPIN to pregnant rats resulted in a decreased survival rate of the newborn and a potential for cataract formation in the survivors. The drug may be used in pregnant women when, in the judgment of the physician, the expected benefits outweigh the potential risk to the fetus.

Usage in Children – The safety and efficacy of this drug in children has not been established. INTROPIN has been used in a limited number of pediatric patients, but such use has been inadequate to fully define proper dosage and limitations for use. Further studies are in progress.

PRECAUTIONS: Avoid Hypovolemia – Prior to treatment with INTROPIN, hypovolemia should be fully corrected, if possible, with either whole blood or plasma as indicated.

Decreased Pulse Pressure – If a disproportionate rise in the diastolic pressure (i.e. a marked decrease in the pulse pressure) is observed in patients receiving INTROPIN, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

Extravasation – INTROPIN should be infused into a large vein whenever possible to prevent the possibility of extravasation into tissue adjacent to the infusion site. Extravasation may cause necrosis and sloughing of surrounding tissue. Large veins of the antecubital fossa are preferred to veins in the dorsum of the hand or ankle. Less suitable infusion sites should be used only if the patient's condition requires immediate attention. The physician should switch to more suitable sites as rapidly as possible. The infusion site should be continuously monitored for free flow.

Occlusive Vascular Disease – Patients with a history of occlusive vascular disease (for example, atherosclerosis, arterial embolism, Raynaud's disease, cold injury, diabetic endarteritis, and Buerger's disease) should be closely monitored for any changes in color or temperature of the skin in the extremities. If a change in skin color or temperature occurs and is thought to be the result of compromised circulation to the extremities, the benefits of continued INTROPIN infusion should be weighed against the risk of possible necrosis. This condition may be reversed by either decreasing or discontinuing the rate of infusion.

IMPORTANT – Antidote for Peripheral Ischemia: To prevent sloughing and necrosis in ischemic areas, the area should be infiltrated as soon as possible with 10 to 15 ml. of Saline solution containing from 5 to 10 mg. of Regitine® (brand of phentolamine), an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, and the solution liberally infiltrated throughout the ischemic area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, phentolamine should be given as soon as possible after the extravasation is noted.

Avoid Cyclopropane or Halogenated Hydrocarbon Anesthetics – Cyclopropane or halogenated hydrocarbon anesthetics increase cardiac autonomic irritability and therefore may sensitize the myocardium to the action of certain intravenously administered catecholamines. This interaction appears to be related both to pressor activity and to beta adrenergic stimulating properties of these catecholamines. Therefore, as with certain other catecholamines, and because of the theoretical arrhythmogenic potential, INTROPIN should be used with EXTREME CAUTION in patients inhaling cyclopropane or halogenated hydrocarbon anesthetics.

Careful Monitoring Required – Close monitoring of the following indices – urine flow, cardiac output and blood pressure – during INTROPIN infusion is necessary as in the case of any adrenergic agent.

ADVERSE REACTIONS: The most frequent adverse reactions observed in clinical evaluation of INTROPIN included ectopic beats, nausea, vomiting, tachycardia, anginal pain, palpitation, dyspnea, headache, hypotension, and vasoconstriction. Other adverse reactions which have been reported infrequently were aberrant conduction, bradycardia, piloerection, widened QRS complex, azotemia, and elevated blood pressure.

DOSAGE AND ADMINISTRATION:

WARNING: This is a potent drug: It must be diluted before administration to patient.

Suggested Dilution – Transfer contents of one ampul (5 ml. containing 200 mg. INTROPIN) by aseptic technique to either a 250 ml. or 500 ml. bottle of one of the following sterile intravenous solutions:

1) Sodium Chloride Injection, USP
2) Dextrose 5% Injection, USP
3) Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
4) 5% Dextrose in 0.45% Sodium Chloride Solution
5) Dextrose (5%) in Lactated Ringer's Solution
6) Sodium Lactate (1/6 Molar) Injection, USP
7) Lactated Ringer's Injection, USP

These dilutions will yield a final concentration for administration as follows:
250 ml. dilution contains 800 mcg./ml. of INTROPIN
500 ml. dilution contains 400 mcg./ml. of INTROPIN

INTROPIN has been found to be stable for a minimum of 24 hours after dilution in the sterile intravenous solutions listed above. However, as with all intravenous admixtures, dilution should be made just prior to administration.

Do **NOT** add INTROPIN Injection to 5% Sodium Bicarbonate or other alkaline intravenous solutions, since the drug is inactivated in alkaline solution.

Rate of Administration – INTROPIN, after dilution, is administered intravenously through a suitable intravenous catheter or needle. An i.v. drip chamber or other suitable metering device is essential for controlling the rate of flow in drops/minute. Each patient must be individually titrated to the desired hemodynamic and/or renal response with INTROPIN. In titrating to the desired increase in systolic blood pressure, the optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the hemodynamic condition is stabilized.

Administration at rates greater than 50 mcg./kg./min. have safely been used in advanced circulatory decompensation states. If unnecessary fluid expansion is of concern, adjustment of drug concentration may be preferred over increasing the flow rate of a less concentrated dilution.

Suggested Regimen:

1. When appropriate, increase blood volume with whole blood or plasma until central venous pressure is 10 to 15 cm H_2O or pulmonary wedge pressure is 14-18 mm Hg.
2. Begin administration of diluted solution at doses of 2-5 mcg./kg./minute INTROPIN in patients who are likely to respond to modest increments of heart force and renal perfusion.

In more seriously ill patients, begin administration of diluted solution at doses of 5 mcg./kg./minute INTROPIN and increase gradually using 5 to 10 mcg./kg./minute increments up to 20 to 50 mcg./kg./minute as needed. If doses of INTROPIN in excess of 50 mcg./kg./minute are required, it is suggested that urine output be checked frequently. Should urine flow begin to decrease in the absence of hypotension, reduction of INTROPIN dosage should be considered. Multiclinic trials have shown that more than 50% of the patients were satisfactorily maintained on doses of INTROPIN less than 20 mcg./kg./minute. In patients who do not respond to these doses with adequate arterial pressures or urine flow, additional increments of INTROPIN may be employed in an effort to produce an appropriate arterial pressure and central perfusion.

3. Treatment of all patients requires constant evaluation of therapy in terms of the blood volume, augmentation of myocardial contractility, and distribution of peripheral perfusion. Dosage of INTROPIN should be adjusted according to the patient's response, with particular attention to diminution of established urine flow rate, increasing tachycardia or development of new dysrhythmias as indices for decreasing or temporarily suspending the dosage.
4. As with all potent intravenously administered drugs, care should be taken to control the rate of administration so as to avoid inadvertent administration of a bolus of drug.

OVERDOSAGE: In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce rate of administration or temporarily discontinue INTROPIN until patient's condition stabilizes. Since INTROPIN's duration of action is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha adrenergic blocking agent, phentolamine, should be considered.

HOW SUPPLIED: 5 ml. ampuls containing 40 mg. dopamine HCl per milliliter. September, 1975

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Exercise Testing for Detection of Myocardial Ischemia in Patients With Abnormal Electrocardiograms at Rest

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This review consists of two parts: (1) discussion of the electrophysiologic mechanisms that are believed to produce ventricular repolarization changes during the electrocardiographic stress test, and (2) clinical assessment of the electrocardiographic changes with stress in patients with an abnormal electrocardiogram at rest. In the first part, the mechanisms of S-T segment elevation, S-T segment depression, T wave changes and linked S-T and T wave changes are reviewed. In the second part, all electrocardiographic abnormalities at rest are grouped into four categories: (1) changes that mask the manifestations of ischemia, (2) changes that simulate or exaggerate the manifestations of ischemia, (3) changes that have no important effect on the manifestations of ischemia, and (4) changes that reproduce the patterns of acute myocardial infarction after an apparent healing. The reported studies of electrocardiographic stress testing in patients who have an abnormal electrocardiogram at rest are summarized.

Detection of myocardial ischemia is the most common purpose of electrocardiographic stress tests in patients with proved or suspected coronary artery disease. The electrocardiographic manifestations of exercise-induced myocardial ischemia consist of transient deviation of the S-T segment from the baseline and sometimes inversion of the U wave. The criteria for positive and negative stress tests have been tested predominantly in persons with a normal electrocardiogram at rest. In patients who have an abnormal electrocardiogram at rest, stress tests have been impeded by concern for patient safety and the difficulty of interpretation of exercise-induced electrocardiographic abnormalities.

In recent years, the safety of electrocardiographic stress tests has been greatly enhanced by monitoring, and several investigators have studied monitored stress tests in the presence of an abnormal electrocardiogram at rest,[1–7] including early convalescence after myocardial infarction.[8] However, the criteria for a positive or negative test and the clinical significance of exercise-induced changes in patients who have an abnormal electrocardiogram at rest have not been fully established.[5,9] In this article we review the published studies of stress testing in persons with an abnormal electrocardiogram at rest and summarize the current state of knowledge in this area. We preface this review by a brief discussion of the electrophysiologic mechanisms believed to produce ventricular repolarization changes during the stress test. Understanding these mechanisms may be helpful in interpreting the studies reviewed.

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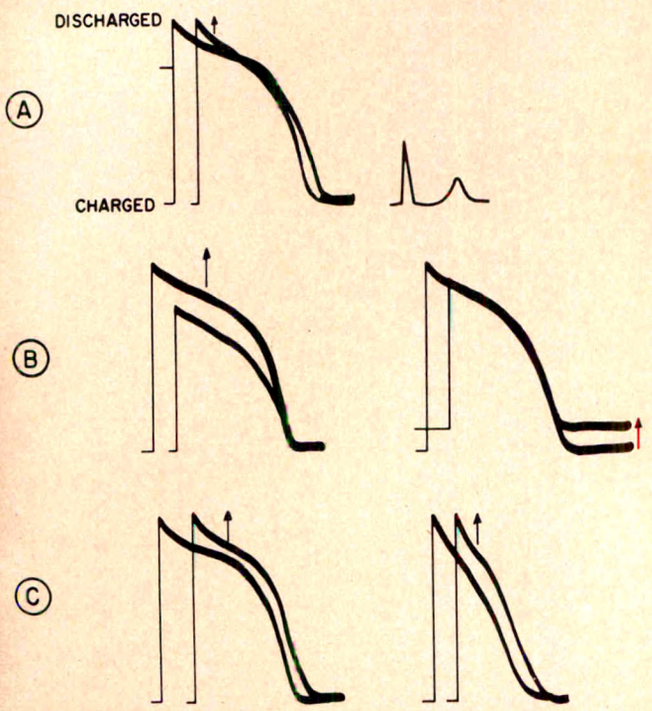


FIGURE 1. Schematic diagrams. **A**, the normal electrocardiogram is derived from the potential differences between two ventricular action potentials. **B**, the potential differences responsible for systolic and diastolic currents of injury. **C**, potential differences responsible for secondary repolarization abnormalities (**at left**) and changes in the repolarization slope (for example, digitalis effect) (**at right**). See text.

Electrophysiologic Mechanism and Differential Diagnosis of Myocardial Ischemia

Transmembrane Action Potential

Potential differences during repolarization responsible for the S-T segment and T wave: Figure 1A is a schematic diagram in which the electrocardiogram is derived from the potential difference between two action potentials hypothetically attributed to the first and last ventricular fibers depolarized during recording of a single QRS complex. In the derived electrocardiogram, the configuration of the S-T segment and T wave is determined by the potential differences during repolarization. The diagram shows that after the end of depolarization some potential differences exist before the onset of uniform depolarization to the level of the plateau. This interval is short but it can cause deviation of the junction ("J depression") and of the early portion of the S-T segment. Because of this, measurements of S-T segment deviation are usually made about 60 to 80 msec after the end of the QRS complex when all ventricular fibers are expected to be depolarized (discharged) to the same membrane potential indicated by two superimposed segments of repolarization before the onset of rapid repolarization (phase 2). The clear space between the rapid repolarizations (phase 3) represents potential differences responsible for the T wave. Afterward, all fibers are "at rest" (charged) and potential differences are absent.

Systolic and diastolic currents of injury: *Figure 1B shows two manifestations of myocardial ischemia:* (1) shortening and decreased amplitude of the action potential, and (2) depolarization, that is, less negative resting membrane potential. The shortening and decreased amplitude will cause potential differences during repolarization, that is, electrical systole, and this will result in systolic current of injury. The depolarization will cause potential differences during electrical diastole that will result in a diastolic current of injury. The left arrow in Figure 1B shows that the potential difference produced by the systolic current of injury will displace the S-T segment; and the right arrow that potential difference produced by the diastolic current of injury will displace the baseline. Both effects will produce the same influence on the electrocardiogram (see later).

S-T deviations in absence of ischemia (secondary repolarization changes): The two diagrams in Figure 1C explain why the entire S-T segment or its major portion may deviate from the baseline in the absence of myocardial ischemia. The diagram on the left shows the mechanism of repolarization abnormalities secondary to conduction delay, indicated by a prolonged interval between the upstrokes of the first and the last action potentials. The longer conduction time lengthens the QRS complex and enhances the potential differences during the entire repolarization because some of the early depolarized fibers begin to pass through the rapid phase 3 repolarization while late depolarized fibers will be still at the level of the plateau. In the diagram, potential differences (arrow) persist throughout the entire repolarization phase and therefore the entire S-T segment deviates from the baseline. Secondary S-T segment changes are usually accompanied by secondary T wave changes.

S-T deviations due to primary repolarization abnormalities in the absence of ischemia: The diagram on the right in Figure 1C shows the mechanism of primary repolarization abnormalities caused by action potentials in which potential differences persist during most or all of repolarization because the slope of repolarization during phase 2 is steeper than normal. This mechanism will cause deviation of the S-T segment from the baseline in the absence of ischemia or any changes in the sequence of depolarization. The short ventricular action potential with a steep slope of repolarization shown in this diagram depicts changes induced by digitalis or tachycardia. This may explain one mechanism of S-T segment depression during exercise-induced tachycardia in the absence of myocardial ischemia. Hypokalemia may cause similar changes in the slope of phase 2, but it also prolongs the duration of the action potential.

S-T deviations due to epicardial or endocardial injury: Figure 2 shows diagrammatically the effects of epicardial and endocardial injury on the S-T segment in the standard limb or anterior precordial leads of the electrocardiogram. Epicardial injury may cause elevation of the S-T segment and depression of the baseline, whereas subendocardial injury may cause depression of the S-T segment or elevation of the baseline. The

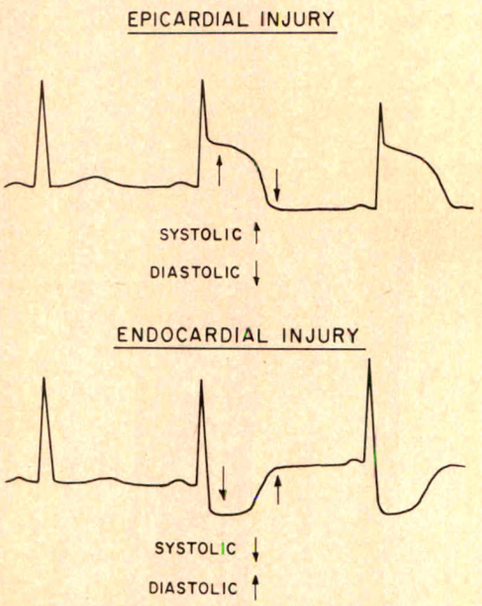


FIGURE 2. Diagram of the effects of subepicardial and subendocardial injury on the S-T segment and the baseline of the electrocardiogram. Note, in this and in the subsequent two figures, that the **direction of arrow** signals the flow of current and not the S-T segment vector. See text.

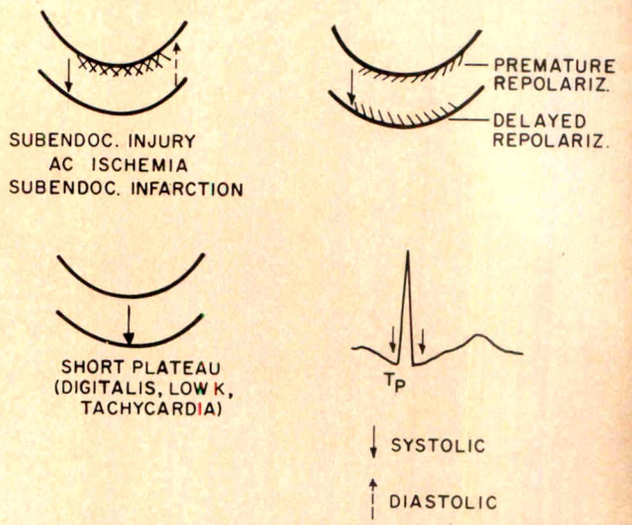


FIGURE 3. Diagram of several mechanisms of S-T segment depression. See text. AC = acute; REPOLARIZ. = repolarization; SUBENDOC. = subendocardial.

conventional electrocardiogram recorded with alternating current coupled amplifiers does not reveal displacement of the baseline, and therefore does not differentiate between the segment displacement caused by the systolic and the diastolic current of injury.

Electrocardiographic Manifestations of Ischemia

Manifestations of ischemia may include depression or elevation of the S-T segment and U wave inversion. T wave changes may also occur but they are not specific.

Depression of S-T segment: S-T depression in precordial leads reflects a posteriorly directed deviation of the S-T segment vector. Several mechanisms of such deviation are shown in schematic diagrams in Figure 3: *In the left upper diagram,* the cross-hatched region represents a region of subendocardial ischemia or infarction that causes a systolic and a diastolic current of injury; the former results in depression of the S-T segment (solid arrow) and the latter in elevation of the baseline (interrupted arrow). *In the upper right diagram,* secondary S-T segment depression is due to delayed repolarization in the subepicardial region, or alternatively to premature repolarization in the subendocardial region. *In the lower left diagram,* S-T segment deviation occurs in the absence of injury or conduction delay, because of the uniform shortening of phase 2 (plateau) of the ventricular action potential, for example, effect of digitalis, hypokalemia or tachycardia. Finally, *the diagram on the lower right* shows that the depression of S-T segment may be caused by atrial repolarization represented by a negative T wave of the P wave (T_p) which is inscribed during the interval between the two arrows. The inscription of atrial repolarization during the S-T segment has been documented in man during recording of atrial monophasic action potentials using suction electrodes.[10] In Figure 3 the negative T_p wave causes a downsloping course of the P-R segment. This sign helps to recognize false positive S-T depression, even though it may be caused not only by a negative T_p wave but also by a P wave superimposed on a U wave.

Elevation of S-T segment: S-T elevation in precordial leads reflects an anteriorly directed deviation of the S-T segment vector. Several mechanisms of such deviation are shown in the schematic diagrams in Figure 4: *In the diagram on the left,* the cross-hatched region represents a region of subepicardial injury, infarction, pericarditis or transient ischemia during variant angina

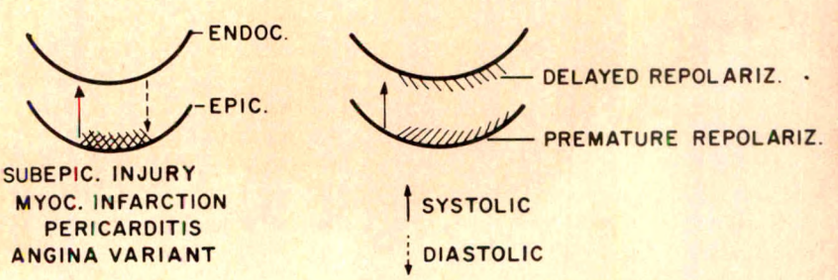


FIGURE 4. Diagram of several mechanisms of S-T segment elevation. See text. ENDOC. = endocardial; EPIC. = epicardial; MYOC. = myocardial; REPOLARIZ. = repolarization; SUBEPIC. = subepicardial.

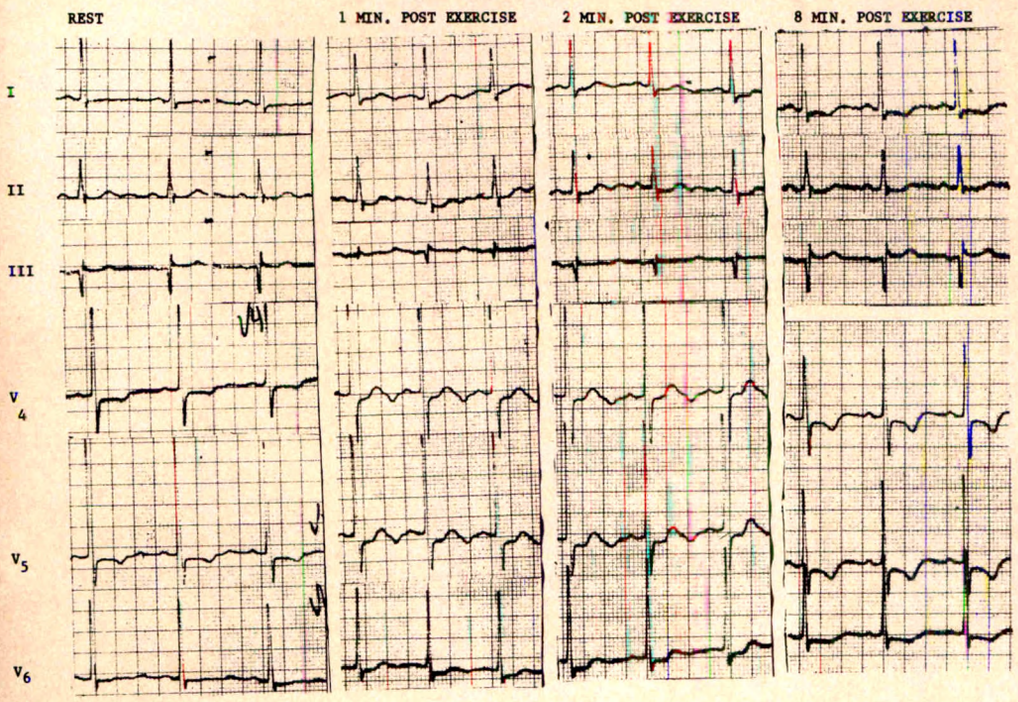


FIGURE 5. U wave inversion in leads V_4 to V_6 during exercise-induced myocardial ischemia and chest pain in a 59 year old man with exertional angina and previous myocardial infarction. The exercise test was stopped after 70 seconds.

pectoris. The resulting systolic and diastolic currents of injury will cause elevation of the S-T segment (solid arrow) and depression of the baseline (interrupted arrow). *In the diagram on the right,* secondary S-T segment elevation is due to delayed repolarization in the subendocardial region, or alternatively to premature repolarization of the subepicardial region. The latter phenomenon is the assumed mechanism of a common normal variant in young persons (see later).

Negative U wave: The mechanism of occasional transient U wave inversion during acute ischemia (Fig. 5) is unknown.

T wave changes: We have stated earlier that the S-T segment reflects potential differences during phase 2, and the T wave represents potential differences during phase 3 of the ventricular action potential. Because these two phases of the action potential differ from each other in their electrophysiologic mechanisms at the cell level, one may expect to encounter differences in the behavior of the S-T segment and the T wave in the surface electrocardiogram. Indeed, as will be discussed later, exercise-induced T wave changes are usually unrelated to the exercise-induced S-T segment changes in persons with or without myocardial ischemia.[7]

Acute ischemic T wave changes: Acute ischemia shortens the duration of the ventricular action potential. This shortening may be expected to cause deviation of the T wave vector toward the ischemic region, but this is seldom clearly recognizable in the surface electrocardiogram, probably because the changes produced by ischemia as such are obscured by several other exercise-induced factors that affect the T wave, such as tachycardia, sympathetic stimulation and hyperkalemia. A very tall upright or a very deeply inverted T wave that frequently appears within seconds or minutes after an acute experimental occlusion in the animal is seldom recorded in man even during the earliest phase of myocardial infarction, probably because during acute ischemia the T wave becomes displaced by the S-T segment deviation. Such T waves are incorporated into the descending limb of the "monophasic" pattern, whereas the Q-T interval is usually shortened.

Postischemic T wave changes: The subsequent "postischemic" T wave abnormalities[11] associated with a prolonged Q-T interval are attributed to prolongation of action potentials in the ventricular myocardium bordering the infarcted area.[12] The postischemic T waves are usually negative in the anterior precordial leads in patients with transmural or nontransmural infarction of the anterior wall and upright in patients with subendocardial or "true" posterior wall infarction. These T wave changes evolve independently of the S-T segment changes produced by ischemia and play no role in the evaluation of the electrocardiographic stress test.[7]

Linked S-T segment and T wave changes: Although during exercise-induced ischemia the S-T segment and the T wave behave independently from each other, different mechanisms of abnormal repolarization frequently cause linked S-T and T wave changes. Such linked changes may justify the electrophysiologically imprecise but clinically useful expression "ST-T changes." Another possible reason for use of this expression is the lack of a distinct point of demarcation between the end of the S-T segment and the onset of T wave. Linked S-T and T wave changes during or after exercise may be expected to occur in association with mechanisms illustrated in the diagrams in Figure 1B, that is, the secondary repolarization abnormalities such as left ventricular hypertrophy or left bundle branch

block, and in Figure 1C, that is, the repolarization abnormalities due to shortening of the plateau of the ventricular action potential such as the effects of digitalis or hypokalemia.

Clinical Assessment of the Stress Test in Patients With an Abnormal Electrocardiogram at Rest

All electrocardiographic abnormalities at rest that require consideration in the evaluation of the stress test may be divided into the following four categories: (1) changes that mask the manifestations of ischemia, (2) changes that simulate or exaggerate the manifestations of ischemia, (3) changes that have no important effect on the manifestations of ischemia, and (4) changes that reproduce the patterns of acute myocardial infarction after an apparent healing (anamnestic response).

Electrocardiographic Manifestations Masking the Manifestations of Ischemia

Intraventricular conduction defects: The electrocardiographic patterns that are probably most frequently responsible for the "false negative" stress test comprise various intraventricular conduction disturbances characterized by the presence of a rightward terminal portion of the QRS complex. This rightward deflection may be directed anteriorly, as in the pattern of right bundle branch block, or posteriorly, as in some patterns of right ventricular hypertrophy or left anterior fascicular block. All such patterns have in common in the left precordial leads, QRS complexes with deep S waves and T waves directed opposite to the S wave. In these complexes the area of the T wave is usually increased, and the S-T segment tends to slope up steeply from the nadir of the S wave to the onset of the T wave. These secondary S-T changes tend to cancel or obscure the characteristic horizontal or downsloping S-T segment course changes induced by myocardial ischemia, and thereby contribute to "false negative" tests. Sometimes, the sensitivity of the stress test in such cases can be enhanced by the selection of the precordial bipolar lead with the maximal R/S ratio. Minor S-T changes are more suggestive of ischemia when they appear in leads with deep S waves than in leads with an R wave of similar amplitude but without an S wave.

Systematic studies of the electrocardiographic pattern with S waves in the left precordial leads are limited to patients with right bundle branch block.[13–15] In one study of right bundle branch block in 40 asymptomatic Air Force crewmen, all had a negative electrocardiographic stress test although eight crewmen had coronary artery disease.[13] Thus, in this study right bundle branch block was associated with "false negative" but not with "false positive" tests. "False negative" tests have been reported also in an earlier study of patients with right bundle branch block.[14] However, in the experience of Ellestad,[15] right bundle branch block does not mask ischemic changes in lead CM_5.

Quinidine and phenothiazines: Another reported cause of "false negative" stress tests is the administration of quinidine.[16] This effect of quinidine could be due to the prolongation of phase 2 of the ventricular action potential by the drug.[17] This may be expected to decrease the repolarization gradient during inscription of the S-T segment and thereby diminish the manifestation of the "injury" currents. The same mechanism could explain the reported "false negative" tests in 5 of 13 patients with coronary artery disease treated with phenothiazines,[6] which cause repolarization changes similar to those produced by quinidine.[17]

Propranolol: McHenry and Morris[18] stated that the most common cause of a change from a positive to a negative test is administration of propranolol, which prevents the appearance of ischemic electrocardiographic changes even when the exercise is continued to the onset of pain. Many other studies[19–23] have shown that administration of propranolol may increase the duration of exercise to the onset of S-T depression or change the stress test from positive to negative. However, these reports do not refer specifically to patients with an abnormal electrocardiogram at rest.

Electrocardiographic Manifestations Simulating or Exaggerating Manifestations of Ischemia

Digitalis: The appearance of a pattern of myocardial ischemia during exercise after administration of digitalis to healthy volunteers was first described in Germany by Zwillinger[24] in 1935 and in this country by Liebow and Feil[25] in 1941. The S-T changes were apparently not due to the vagal action of digitalis because they were not altered by administration of atropine.[26] Nordström-Öhrberg[27] found S-T segment or T wave abnormalities, or both, in 89 percent of 64 healthy volunteers treated with digitalis. Detailed analysis of these abnormalities showed most commonly a horizontal or downsloping depression of the S-T segment associated with a diphasic or negative T wave; lowering of the T wave alone, junctional S-T segment depression or a concave S-T segment with maximal depression in the middle of the segment was less common.[27]

Several later studies firmly established the role of digitalis in producing abnormal responses to exercise in persons without myocardial ischemia and in exaggerating abnormalities induced by ischemia.[3,4,6,15,28–34] The effects of digitalis on the exercise electrocardiogram are not modified by administration of nitroglycerin or oxygen but disappear when the drug is eliminated from the body.[31] In persons receiving long-acting preparations such as digitoxin, exercise-induced electrocardiographic abnormalities may be present as long as 3 weeks after the administration of the last dose.[29]

Recently, some investigators have suggested that digitalis does not interfere with evaluation of the electrocardiographic stress test if the criteria for a positive test are appropriately modified. Thus, Nasrallah et al.[35] reported that myocardial ischemia can be suspected in patients treated with digitalis if the depression of the S-T segment exceeds 0.15 mv. Other investigators[36] considered the test positive when the S-T segment depression exceeded 0.2 mv. Further studies are needed

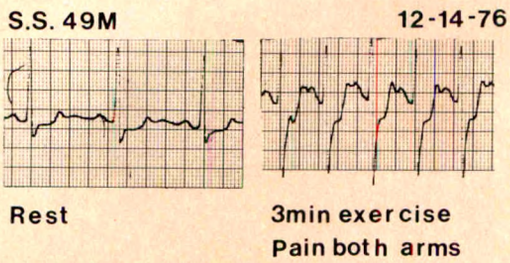


FIGURE 6. Increase in S-T segment depression induced by 3 minutes of exercise in a 49 year old man treated with digitalis. The patient had rheumatic heart disease, and mitral valve replacement was performed in 1968. Cardiac catheterization 2 weeks after the exercise test revealed malfunction of the prosthetic valve, pulmonary hypertension and normal coronary angiogram. See text.

to test the specificity and sensitivity of these newly proposed criteria. Figure 6 shows S-T segment depression of 0.1 mv at rest and of 0.5 mv after exercise in a patient who had a normal coronary arteriogram. Absence of S-T depression during strenuous exercise in patients treated with digitalis increases the probability that the test is indeed negative.[15]

Other drugs: False positive tests have been reported in a small number of patients treated with diuretic drugs, alpha methyldopa and diazepam.[6,34] Further studies in a larger number of patients will be required to assess the clinical significance of these observations.

Pattern of left ventricular hypertrophy: False positive tests in the presence of a pattern of left ventricular hypertrophy have been frequently reported both without and with secondary repolarization abnormalities.[2,3,6,11,37,38] Therefore, in the presence of such a pattern, exercise-induced appearance of S-T segment depression or increased depth of preexisting S-T depression should not be interpreted as evidence of a positive test.

Left bundle branch block: A pattern of left bundle branch block is associated with pronounced secondary repolarization abnormalities. In some studies[39,40] the appearance of additional exercise-induced S-T segment changes did not discriminate between persons with and without coronary artery disease, but in one study[41] coronary artery disease was present in all patients with left bundle branch block who had additional depression of the S-T segment of 0.15 mv or more during the submaximal exercise test.

Wolff-Parkinson-White pattern: Several studies[12,42,43] have shown that secondary repolarization abnormalities caused by preexcitation interfere with the interpretation of exercise-induced changes in patients with the Wolff-Parkinson-White pattern.

Short P-R segment: False positive tests associated with depression of both the junction (J point) and the S-T segment have been reported in patients with a short P-R segment.[44] Atrial repolarization has been suggested as one of the possible mechanisms of such changes.[39]

Hypokalemia: Hypokalemia can introduce error in interpretation of the electrocardiographic stress test,[45,46] and electrocardiographic signs of hypokalemia can appear during exercise even in patients whose electrocardiogram at rest is not diagnostic of hypokalemia.[45] In some patients treated with thiazide diuretic agents exercise-induced signs of hypokalemia that were present when serum potassium was at the low, normal or borderline level disappeared after potassium repletion.[45]

Myxedema: Reversible exercise-induced T wave abnormalities and sagging S-T segments have been observed in patients with myxedema.[47]

Depression of S-T segment in the electrocardiogram at rest: Horizontal or slightly downsloping S-T segment depression may occur as an apparent normal variant in the absence of ischemia, digitalis, hypokalemia or secondary repolarization abnormalities. This variant occurs more commonly in women than in men.[48]

Several investigators have reported increased depression of the S-T segment and false positive tests when the S-T segment was depressed at rest.[2,6,48,49] We have made similar observations. However, in one recent study[50] preexisting 0.05 mv S-T segment depression at rest did not decrease the sensitivity or the specificity of the stress test. In this study, obstructive coronary artery disease was present in 23 of 26 patients with exercise-induced additional S-T segment depression and in only 2 of 11 patients (10 women) without such exercise-induced additional depression.

Effect of carbon monoxide: In an interesting case recently reported,[51] breathing air polluted with carbon monoxide caused a positive exercise test in a healthy person who had a negative exercise test while he was breathing pure compressed air. Similar mechanisms may be responsible for positive exercise tests after cigarette smoking.[10]

Effect of heart disease: The reported results of exercise tests in patients with hypertensive and rheumatic heart disease[37,52–54] are difficult to evaluate because some of the patients were treated with digitalis and others had arrhythmias or abnormal electrocardiographic patterns at rest. However, the presence of heart disease can by various mechanisms contribute to a positive test even when the electrocardiogram is normal at rest: Exercise may induce myocardial ischemia by unbalancing the supply and demand of oxygen, produce intraventricular conduction disturbances or unmask secondary repolarization abnormalities caused by hypertrophy. Wong et al.[37] found S-T segment depression greater than 0.1 mv after maximal exercise tests in 32 percent of hypertensive patients but in only 8 percent of normotensive control subjects. In the presence of mitral valve prolapse, exercise-induced S-T segment depression has been reported in several patients who had normal coronary arteriograms[55,56] and either normal or abnormal T waves at rest.[55,56]

Orthostatic changes: We have routinely recorded the electrocardiogram with patients in the upright position before each exercise test for the past 25 years. Our previous study[33] showed that orthostatic abnormalities confined to the T wave are more common than abnor-

malities of either the S-T segment alone or combinations of S-T segment and T wave abnormalities. We also found that when the orthostatic S-T segment changes were induced in patients who had positive stress tests such changes were less pronounced than the exercise-induced S-T segment changes of ischemia. In our experience orthostatic changes have not simulated myocardial ischemia. However, Friesinger et al.[57] reported on several patients with orthostatic T wave abnormalities who had exercise-induced S-T segment depression greater than 0.1 mv but normal coronary arteriograms. These findings were associated with the presence of chest pain, easy fatigability and other manifestations ascribed to "vasoregulatory abnormalities."[57]

Hyperventilation abnormalities: In our laboratory the electrocardiogram is recorded routinely after 30 seconds of vigorous hyperventilation before each diagnostic stress test is performed. In our experience[58] hyperventilation seldom induces S-T segment depression. However, we could induce flattening and inversion of the T wave by vigorous hyperventilation in the majority of healthy persons whose electrocardiogram was normal at rest.[58] Several investigators[59–61] described electrocardiographic changes during hyperventilation that were identical to those of myocardial ischemia in patients whose coronary arteriograms were normal. Such cases exemplify the clinical usefulness of routine hyperventilation tests before exercise.[54,59]

Electrocardiographic Abnormalities That Have No Important Effects on the Manifestation of Ischemia

Isolated primary T wave abnormalities: T wave abnormalities that occur in the absence of QRS changes are considered primary. They may be caused by healed nontransmural or transmural infarction, pericarditis and a host of neurogenic, endocrine and unidentified "functional" factors.[62] Several recent studies[3,6,7,63] have shown that the behavior of the T wave during exercise is similar in patients with and without ischemic heart disease, and that T wave abnormalities at rest do not influence the incidence of positive and negative responses to exercise. Aravindakshan et al.[7] evaluated the results of submaximal exercise tests in six electrocardiographic leads recorded simultaneously in two groups of patients with T wave abnormalities in one or more of leads I, II and V_4 to V_6. Group I included 185 patients with documented ischemic heart disease, and Group II 28 patients in whom ischemic heart disease appeared unlikely. The test was positive in 88 percent in Group I and in 4 percent in Group II. In the majority of patients in both groups the T wave either did not change or became more positive or less negative, that is, less "abnormal" after exercise. The pattern of exercise-induced T wave changes was similar in patients with and without ischemic heart disease, and was influenced predominantly by the physiologic effects of exercise. T wave normalization after exercise occurred frequently in patients both with and without ischemic heart disease and in patients with positive and negative exercise tests. These results indicate that T wave abnormalities, not caused by hypertrophy, conduction disturbances, drugs or electrolyte imbalance, do not modify the results of the submaximal electrocardiographic stress test, and that behavior of the T wave after exercise does not alter the interpretation of the postexercise electrocardiogram. The independent behavior of the S-T segment and T wave after exercise is consistent with the theory that the S-T segment and the T wave are generated by different components of the ventricular action potential.[7,62]

S-T segment elevation attributed to "premature repolarization": S-T segment elevation at rest in one or more leads in the absence of heart disease is a normal variant that occurs predominantly in young men, and more commonly in black than in white men. In our experience S-T segment elevation disappears or becomes less pronounced during exercise-induced tachycardia (unpublished observations).

Changes That Reproduce the Pattern of Acute Injury in Patients With Healed Myocardial Infarction

Although several investigators[64,65] have considered transient S-T segment elevation during or after exercise a manifestation of myocardial ischemia, the clinical significance of this phenomenon in patients with healed myocardial infarction is not always clear. It has been shown[66] that the time course of regression of S-T segment elevation after infarction varies considerably in different patients and that in some patients S-T elevation persists for months or years. The persistence of S-T segment elevation after myocardial infarction is frequently associated with the presence of ventricular aneurysm or dyskinetic motion of the infarcted region. Recent studies showed that in some patients with dyskinesia of the infarcted segments, the S-T segment was isoelectric at rest but became elevated during exercise-induced tachycardia. The electrophysiologic mechanism of exercise-induced S-T segment elevation in patients with ventricular aneurysm is not well understood. However, unlike the S-T elevation associated with the variant angina pectoris syndrome, that associated with ventricular dyskinesia is usually painless.

We propose the term "anamnestic response" to characterize the transient reappearance of the pattern of acute injury of the initial stage of myocardial infarction during tachycardia. The study of Atterhög et al.[8] showed that such responses are more common during the early stage after myocardial infarction. Thus, serial exercise tests produced S-T elevation in 10 of 12 patients studied within 3 weeks and in only 3 of these patients within 12 to 18 months after the onset of infarction. The "anamnestic" S-T segment response may be expected to produce S-T elevation in anterior chest leads in patients with healed anterior wall infarction and S-T depression in patients with inferior or posterior infarction. In keeping with this expectation, Kelemen et al.[67] found exercise-induced "ischemic" S-T segment changes in 6 of 10 patients with healed inferior or posterior infarction and in only 1 of 8 patients with isolated anterior or combined anterior-inferior infarction. Recently, Simoons et al.[68] found an increased inferiorly

directed S-T segment deviation in patients with old inferior infarction and an increased anteriorly directed S-T deviation in patients with old anterior infarction. They considered dyssynergy a factor that can influence the behavior of the S-T segment independently of ischemia. Chahine et al.[69] described exercise-induced S-T segment elevation in 29 of 840 patients (3.5 percent). Of these 29, left ventricular aneurysm was present in 86 percent. Conversely, exercise-induced S-T segment elevation appeared in 18 of 28 patients (64 percent) with left ventricular aneurysm. These results suggest that exercise-induced S-T segment elevation may reflect the presence of abnormal wall motion in the area of past infarction. A similar view was expressed by Ellestad[15] and Kattus.[4] At present, the electrophysiologic mechanism of the exercise-induced "anamnestic" reproduction of a pattern of acute injury in patients with myocardial aneurysms and scars remains obscure, mainly because we lack understanding of the general mechanism by which an abnormal left ventricular motion causes deviation of the S-T segment.

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Musical Murmurs: An Echo-Phonocardiographic Study

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Five patients with musical murmurs were studied noninvasively with simultaneous echocardiography and phonocardiography. Three patients had aortic regurgitation, one mitral regurgitation and one tricuspid regurgitation. The frequency of the musical murmurs ranged from 40 to 158 cycles/sec. The patient with tricuspid regurgitation manifested an inspiratory honk. Simultaneous echo-phonocardiography revealed regular valve leaflet flutter (aortic, mitral or tricuspid) at a frequency identical to that of the simultaneously recorded musical murmur. This study demonstrates that echocardiography is a useful noninvasive tool in identifying the site of origin of musical murmurs.

Musical murmurs constitute a unique auscultatory sign in patients with a variety of cardiac abnormalities.[1–5] Although musical murmurs have been associated with specific valve abnormalities, there is no universally accepted unified concept of their production.[1–6] Two theories previously proposed include regular vibrations of an elastic structure (for example, part of or the whole valve leaflet related to decreased valve support, aberrant chordae tendineae) and sound production related to fluids flowing past an obstruction (vortex shedding).[4,6] To our knowledge neither of these mechanisms has been demonstrated in a series of patients with musical murmurs arising from different valves. During the past 2 years we used a simultaneous recording of echocardiograms and phonocardiograms to study five patients with musical murmurs. The focus of our study was to (1) correlate valve motion and phonocardiographic recordings in a series of patients with musical murmurs, and (2) demonstrate the value of echocardiography in identifying noninvasively the site of origin of these murmurs.

Methods

Simultaneous echocardiograms and phonocardiograms were obtained using a Unirad 100 series instrument interfaced with a Cambridge Fiberoptic Recorder. A 2.25 megahertz transducer, 13 mm in diameter and focused at 7.5 cm was used. The echocardiograms were obtained with the standard left parasternal approach (Patients 1, 2, 4 and 5) or with a subxiphoid approach (Patient 3). Phonocardiograms were recorded at the second or third left intercostal space (Patients 1, 2 and 3), the lower left sternal border (Patient 4) or the apex (Patient 5).

Results

Seven patients with musical murmurs were referred to our noninvasive cardiac laboratory during a 2 year period (January 1975 to December 1976). Two patients were excluded from the study because adequate echocardiograms could not be obtained. The other five patients were three men and two women, aged 22 to 75 years (mean 49.8). Aortic regurgitation was present in three patients, tricuspid regurgitation in one and mitral regurgitation in one. The echocardiographic data are summarized in Table I. The clinical and echocardiographic findings are discussed briefly for individual patients.

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Patient 1: This 22 year old black man had aortic regurgitation secondary to rheumatic heart disease. Physical findings included cardiomegaly, a grade 5/6 musical holodiastolic murmur heard all over the precordium, collapsing pulse and pistol shot sounds. In the phonocardiogram, the first and second heart sounds could not be identified. A holodiastolic musical murmur was recorded at a frequency of 130 cycles/sec initially, decreasing to a frequency of 95 cycles/sec in late diastole. In the echocardiogram, only the anterior cusp of the aortic valve was visualized during systole. In diastole, the normally thin mid aortic line, representing apposition of the valve cusps, was replaced by a band of echoes showing regular vibrations of the aortic valve cusps at the same frequency as the murmur. Terminal slowing of the frequency was also evident in the aortic valve vibrations. The anterior mitral valve leaflet showed coarse flutter in diastole. Mitral valve closure was normal. In addition, abnormal echoes, consistent with aortic valve prolapse, were seen in the left ventricular outflow tract.

Patient 2 (Fig. 1): A 64 year old black man with aortic regurgitation due to syphilitic heart disease was evaluated. Physical findings consisted of cardiomegaly and a grade 6/6 holodiastolic musical murmur radiating over the spine, the top of the head and the radial styloids. The phonocardiogram revealed markedly diminished first and second heart sounds. A musical holodiastolic murmur was recorded at a frequency of 130 cycles/sec initially and a frequency of 90 cycles/sec in end-diastole. In the echocardiogram, the anterior and posterior aortic valve cusps showed irregular systolic fluttering. During diastole, a band of echoes, demonstrating regular flutter of the aortic valve cusps, was seen. The frequency patterns of the murmur and cusp flutter were identical. The anterior mitral valve leaflet showed diastolic flutter characteristic of aortic regurgitation. Mitral valve closure was normal.

Patient 3: This 22 year old white woman exhibited Marfan's syndrome and aortic regurgitation. Significant findings included pectus excavatum, a grade 2/6 systolic murmur and a grade 5/6 holodiastolic murmur, with a musical quality during early diastole, heard best at the second left intercostal space. The phonocardiogram revealed a diminished first heart sound followed by an ejection click. An ejection systolic murmur and a holodiastolic murmur were seen. The early diastolic portion of the murmur had a dominant frequency of 40 cycles/sec. The echocardiogram suggested the presence of a bicuspid aortic valve. During diastole, the aortic cusps showed regular flutter at a frequency of 40 cycles/sec. The anterior mitral valve leaflet showed diastolic flutter. There was no evidence of early mitral valve closure.

TABLE I

Echocardiographic Data

Case no.	$LVID_D$ (cm)	$LVID_S$ (cm)	% Fiber Shortening	Wall Thickness IVS (cm)	Wall Thickness LVPW (cm)	LAD (cm)	AR (cm)
1	6.7	3.6	47	1.0	1.0	4.3	3.5
2	6.3	3.9	38	1.2	1.1	4.5	2.8
3	4.5	2.5	44	0.5	0.7	3.4	3.3
4	3.9	2.1	46	1.1	1.1	3.8	3.8
5	5.2	2.6	50	0.9	0.9	4.9	2.3

AR = aortic root; IVS = interventricular septum; LAD = left atrial dimension; $LVID_D$ and $LVID_S$ = left ventricular end-diastolic and end-systolic internal diameter, respectively; LVPW = left ventricular posterior wall.

Patient 4 (Fig. 2): A 66 year old black man with chronic cor pulmonale and tricuspid insufficiency was evaluated. Physical findings consisted of a closely split second heart sound with a loud pulmonary component and a faint systolic murmur at the lower left sternal border that became a loud systolic honk during inspiration. The phonocardiogram revealed a faint systolic murmur during expiration. During inspiration, a holosystolic murmur (honk) with a frequency of 90 cycles/sec appeared. The simultaneously recorded echocardiogram revealed regular flutter of the anterior leaflet of the tricuspid valve during systole, at a frequency identical to that of the murmur. The simultaneously recorded mitral valve did not

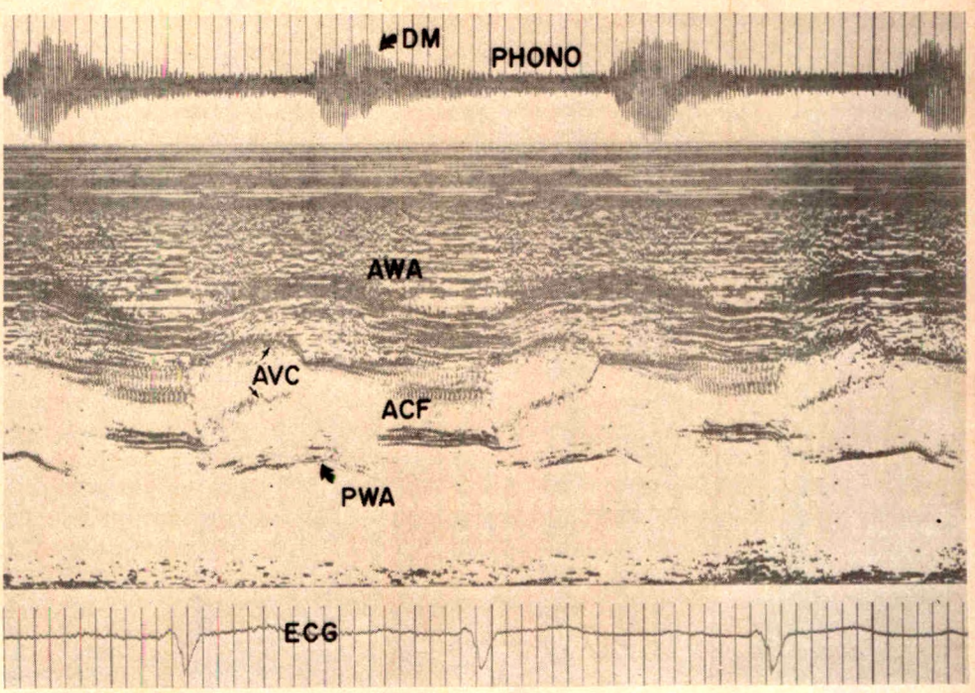


FIGURE 1. Case 2. Simultaneous echocardiogram and phonocardiogram. Paper speed is 100 mm/sec. The phonocardiogram (PHONO) reveals a holodiastolic musical murmur with a frequency of 130 cycles/sec initially and 90 cycles/sec in end-diastole. The echocardiogram of the aortic root reveals coarse fluttering of the aortic valve cusps (AVC) during systole. During diastole a band of echoes, consisting of regular fluttering of the aortic valve cusp (ACF) at the same frequency as the murmur, is seen. The terminal decrease in frequency is obvious in the murmur as well as in the aortic valve flutter. AWA = anterior aortic wall; DM = diastolic murmur; ECG = electrocardiogram; PWA = posterior aortic wall.

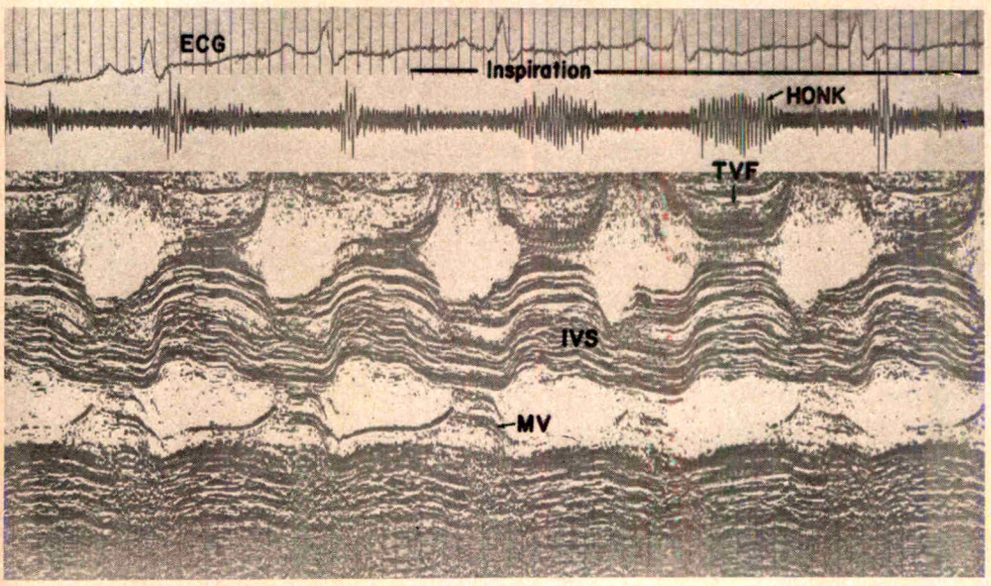


FIGURE 2. Case 4. The phonocardiogram demonstrates the appearance of a holosystolic murmur (honk) at a frequency of 90 cycles/sec during inspiration. Paper speed is 100 mm/sec. The simultaneous echocardiogram reveals flutter of the anterior leaflet of the tricuspid valve (TVF) at an identical frequency. Note that the tricuspid valve flutter is absent during expiration. ECG = electrocardiogram; IVS = interventricular septum; MV = mitral valve.

show any flutter. During expiration, both the murmur and the tricuspid leaflet flutter were absent.

Patient 5: A 75 year old black woman presented with a history of old inferior wall myocardial infarction and mitral regurgitation. Significant findings consisted of a systolic thrill and a grade 4/6 musical holosystolic murmur at the apex. The phonocardiogram demonstrated diminished first and second heart sounds at the apex. A musical holosystolic murmur (honk) was recorded at a frequency of 158 cycles/sec. The echocardiogram revealed regular systolic flutter of the mitral leaflets at a frequency identical to that of the murmur. The tricuspid valve echogram did not reveal any evidence of flutter during systole.

Discussion

Musical murmur: Murmurs can be classified into musical and nonmusical murmurs. Various metaphors have been used to describe musical murmurs, including "sea-gull cry" and "dove-coo murmur."[4,7] Honks and whoops are musical murmurs named because of their likeness to the noise made by geese and the whoop of whooping cough.[1,2,3,5] Phonocardiographically, musical murmurs consist of virtually pure sine wave oscillations whereas nonmusical murmurs are composed of a mixture of frequencies.[4]

The exact mechanism by which musical murmurs are produced is unknown. Postmortem evidence of the presence of a structure that could vibrate in the bloodstream in a regular periodic fashion has led investigators to postulate that musical murmurs are secondary to the vibrations of an elastic structure.[7,8] The classic example of this kind is the retroverted aortic cusp.

Valve vibrations and flutter as cause of musical murmurs: Using the technique of simultaneous echocardiography and phonocardiography, our study documented that such valve vibrations do occur in patients with musical murmurs. The fundamental frequencies of the murmur and the valve vibrations were similar in our five cases. The demonstration of these findings in aortic, mitral and tricuspid valves establishes echocardiography as a valuable noninvasive tool for localizing the origin of both systolic and diastolic musical murmurs from various valves. In all our patients, the source of the musical murmur could be determined from the physical examination and confirmed with echocardiography. In cases that present confusing auscultatory findings, this technique may prove to be a valuable method of localizing the source of the murmur. However, it may be of limited value in patients with atrial fibrillation or flutter, in whom differentiation of valve flutter related to the arrhythmia might prove impossible.

Previous workers[9,10] have demonstrated valve abnormalities in the echocardiograms of patients with musical murmurs. Felner et al.[9] showed that musical murmurs might be associated with echocardiographic features of mitral valve prolapse. Chandraratna et al.[10] demonstrated aortic valve fluttering in a patient with a musical murmur but did not use the technique of combined echo-phonocardiography.

McKusick[8] related the origin of musical murmurs to valve vibration. Our echo-phonocardiographic demonstration of valve flutter and of musical murmurs with similar frequencies lends credence to this hypothesis. Bruns[6] believed that musical murmurs might be produced by eddy currents developed from fluid flowing around an obstruction and its associated trailing vortexes. He assumed that any vibrations of the containing structures of the cardiovascular system were secondary to those forces. Bruns recognized that vibrations of an elastic structure, although secondary, were an efficient generator of sound and might accentuate the murmur. Despite the demonstration of leaflet flutter, our data cannot establish whether the valve flutter is primary or secondary. However, we hypothesize that the primary source of murmur production is an intrinsic leaflet abnormality that allows leaflet vibration. In the presence of the leaflet abnormality, the proper hemodynamic milieu will provide the initiating flow pattern that leads to leaflet flutter and murmur generation.

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Familial Study of Hypertrophic Cardiomyopathy and Congenital Aortic Valve Disease

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A woman with coexisting calcific aortic valve disease and hypertrophic obstructive cardiomyopathy was studied before homograft replacement of the aortic valve and in the second and fourth postoperative years. Postoperative hemodynamic findings, in studies performed with and without pharmacologic agents, were similar to those of patients with hypertrophic cardiomyopathy. Echocardiographic studies 9 years after operation revealed asymmetric septal hypertrophy and systolic anterior motion of the mitral valve leaflet echoes. The patient eventually died from carcinoma of the bronchus 9 years after aortic valve replacement. At autopsy the heart showed the features of hypertrophic obstructive cardiomyopathy. In addition, in the aorta the arrangement of the smooth muscle and elastic fibers was disordered.

Subsequently, 10 asymptomatic relatives from four generations of this family were studied clinically and with echocardiography. Unsuspected asymmetric septal hypertrophy was found in four, and the pattern of the aortic valve echoes was compatible with a bicuspid valve in three. Three relatives had coexisting asymmetric septal hypertrophy and a bicuspid aortic valve. This family study shows that hypertrophic cardiomyopathy and bicuspid aortic valve may coexist and may be inherited as a dominant characteristic with variable manifestations.

The coexistence of hypertrophic cardiomyopathy and fixed aortic valve disease as assessed from hemodynamic, anatomic and echocardiographic criteria has been frequently reported.[1–9] We have been unable to trace reports of a histologically documented hypertrophic cardiomyopathy coexisting with congenital bicuspid aortic valve and an aorta with an abnormal histologic structure. This clinical and echocardiographic study of 10 relatives from four generations of one family demonstrates a possible familial inheritance and coexistence of hypertrophic cardiomyopathy and a bicuspid aortic valve. The investigation was prompted by the finding of classic echocardiographic and histologic abnormalities of hypertrophic cardiomyopathy in a patient who, 9 years before death, had an aortic homograft replacement for calcific aortic disease thought to be congenital in origin.

Material and Methods

The material consisted of the propositus, a woman with calcific aortic valve disease and hypertrophic cardiomyopathy, and 10 relatives from four generations of her family. The hemodynamic, angiographic, operative, echocardiographic and autopsy data of this case are described. Ten of 11 relatives were available for study; all 10 were asymptomatic. The one relative who was not examined had a history of heart disease of unknown origin. There was no evidence of consanguineous marriage. The pedigree is shown in Figure 1. All relatives were examined clinically and studied with a 12 lead electrocardiogram, phonocardiogram and echocardiogram, as described previously.[9,10] The interventricular septal to posterior left ventricular wall thickness ratio was calculated at the level of the

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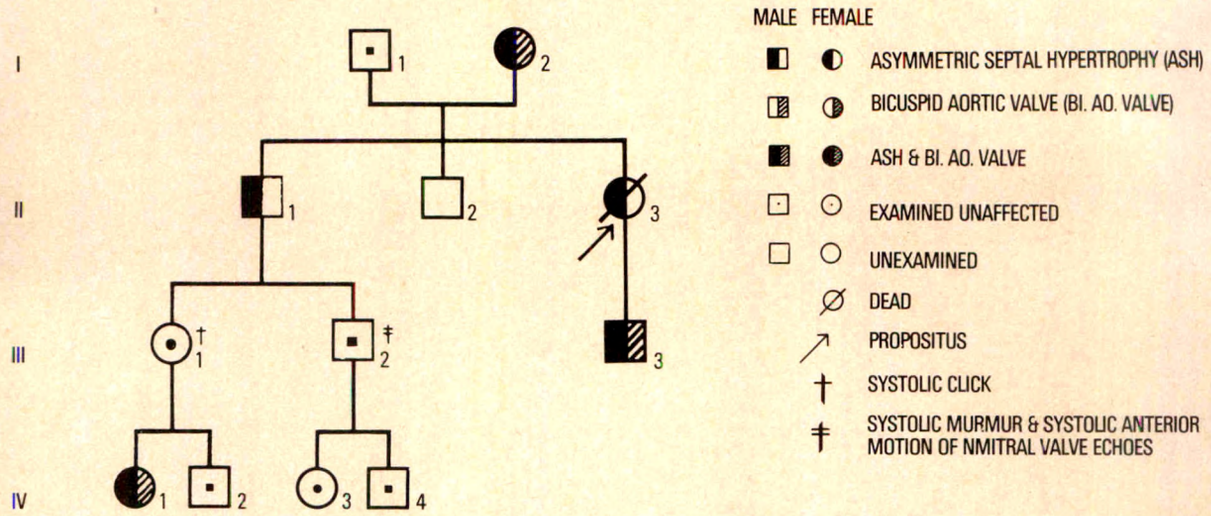


FIGURE 1. Pedigree of propositus (Case II 3) showing cardiac disease diagnosed in 10 members of her family.

tips of the mitral valve leaflet echoes. A ratio of 1:3 or greater was accepted as evidence of asymmetric septal hypertrophy.

The echocardiographic criterion for a suspected bicuspid aortic valve was an aortic cusp eccentric index (EI) of 1.25 or greater during diastole in three or more consecutive cardiac cycles. To avoid false positive findings, measurements were taken only when the aortic root and cusp echoes were clearly defined. The eccentric index was calculated as described by Nanda et al.[11]:

$$EI = \frac{\text{1/2 width of aortic lumen}}{\text{minimal distance of the cusp echo to the nearest aortic margin.}}$$

Results

Propositus

Clinical data: A 48 year old woman, previously asymptomatic, presented at age 39 with effort angina pectoris and dyspnea associated with palpitations. A cardiac murmur had been noted at age 16 years. There was no history of rheumatic fever. The clinical signs were those of mixed aortic valve disease. At cardiac catheterization the aortic valve gradient was 120 mm Hg. An aortogram (with injection into the aortic root) revealed mild aortic regurgitation and large unobstructed coronary arteries. In addition, a trivial resting diastolic mitral valve gradient of 3 mm Hg was found. The left ventriculogram revealed severe left ventricular hypertrophy with almost complete obliteration of the cavity during end-systole. There was no evidence of mitral regurgitation. The aortic valve appeared thick and rigid.

The patient subsequently underwent homograft replacement of the aortic valve. At operation, the aortic valve was noted to have a small triangular orifice measuring 0.5 cm with nodular calcification of the cusps. However, pathologic examination of the valve after its removal in one complete portion suggested a congenitally abnormal valve that was fundamentally bicuspid because the cusps were of different sizes. The mitral valve was not apparently stenosed, although the chordae tendineae and leaflets were thickened; a dilator set at 3.5 cm easily passed through the valve orifice. This suggests that the small mitral valve gradient found during the preop-

TABLE I

Hemodynamic Data on Case II 3 (Propositus)

	Time of Study	At Rest	Post-Ectopic	Isoproterenol Pre	Isoproterenol Post	Propranolol Pre	Propranolol Post	LV Angiogram Pre	LV Angiogram Immediately Post
LV pressure S/D (mg Hg)	Preop*	200/12	—	—	—	—	—	—	—
	Postop, 2 yr	150/20	175/20	150/20	180/20	150/20	150/20	150/20	—
	Postop, 4 yr	150/20	185/20	150/20	200/10	150/15	150/17	150/20	125/20
Femoral arterial pressure S/D (mm Hg)	Preop	80/50	—	—	—	—	—	—	—
	Postop, 2 yr	125/55	125/50	125/50	125/50	125/50	125/50	150/50	—
	Postop, 4 yr	125/60	120/50	125/60	115/50	115/50	110/50	112/50	85/50
LVOT systolic pressure gradient (mm Hg) (heart rate/min)	Preop	120 (65)	—	—	—	—	—	—	—
	Postop, 2 yr	25 (75)	50 (75)	25 (75)	55 (96)	25 (78)	25 (65)	25 (65)	—
	Postop, 4 yr	25 (75)	65 (75)	25 (70)	85 (110)	35 (65)	35 (60)	35 (62)	40 (110)

*Preoperative study also showed a mitral valve diastolic gradient of 3 mm Hg at rest.
— = not recorded; LV = left ventricular; LVOT = left ventricular outflow tract; post = after; postop = postoperative; pre = before; preop = preoperative; S/D = systolic/diastolic.

erative hemodynamic study was due to left ventricular inflow tract obstruction at the level of the mitral valve associated with interventricular septal hypertrophy and incomplete mitral valve opening.[9,12] An unexpected finding was a muscular subvalve stenosis of the left ventricle with gross septal hypertrophy extending to the mitral valve leaflet; the surgeon (Donald Ross) reported that his finger was tightly gripped in the subvalve region.

The aortic valve was replaced with a freeze-dried homograft valve. No myotomy or myectomy was performed. The immediate postoperative period was difficult because of various tachyarrhythmias and a reduced cardiac output that in retrospect was thought to be due in part to the unrelieved subvalve obstruction.

The patient made a good recovery, subsequently remaining symptom-free on a regimen of propranolol and treatment to prevent heart failure. Throughout the 9 years of postoperative follow-up studies, she had a third heart sound, a grade 2/6 pansystolic murmur at the apex and a grade 3/6 ejection murmur at the left sternal edge. The patient ultimately died from bronchogenic carcinoma. Autopsy was performed and the whole heart was available for examination.

Cardiac catheterization: This procedure was carried out before the operation and again in the 2nd and 4th postoperative years. Simultaneous left ventricular and femoral arterial pressures were recorded (Table I). The postoperative studies showed an increase of the peak systolic left ventricular outflow tract gradient after an ectopic beat and after intravenous administration of 2 μg of isoproterenol. Intravenous administration of 2 μg of propranolol did not alter the gradient.

The left ventriculogram (Fig. 2) 2 years after operation showed obliteration of the apex and the mid portion of the left ventricular cavity at end-systole. In addition, there was mild mitral regurgitation. The second postoperative left ventriculogram (4 years after operation) was identical with the first.

Electrocardiograms: The preoperative and 1 month postoperative electrocardiograms were identical and revealed sinus rhythm with tall R waves, S-T segment depression and deep symmetrical T wave inversion in leads I, II, aVL, aVF and V_3 to V_6. These changes indicated left ventricular hypertrophy and were progressive from the 3rd to the 9th postoperative years.

Echocardiograms: These studies were carried out 9 years after aortic valve replacement. Figure 3, A and B, shows asymmetric septal hypertrophy at the submitral and mitral valve levels. In addition, abnormal systolic anterior motion of the mitral valve leaflet echoes is shown during systole. These patterns are considered pathognomonic of hypertrophic cardiomyopathy. The normal aortic valve echogram from the homograft valve is shown in Figure 3C.

Pathologic data: The heart was enlarged (weight 460 g) and showed features of hypertrophic cardiomyopathy with a small left ventricular cavity. The interventricular septum was hypertrophied and bulged into both the aortic and pulmonary outflow tracts (Fig. 4). In particular, the septum was thickened in its upper half, measuring 2.5 cm across (specimen fixed), and, where it bulged into the aortic outflow tract, there was an area of subaortic endocardial fibrosis, whose outline was a mirror image of the anterior cusp of the mitral valve. In addition, this thickened septum appeared to have made contact with the chordae tendineae of the anterior cusp of the mitral valve, resulting in fibrous thickening (described later). The left ventricular free wall was also hypertrophied and measured approximately 1.5 cm, but the thickening was considerably less than that present in the interventricular septum. Both the anterior and posterior papillary muscles

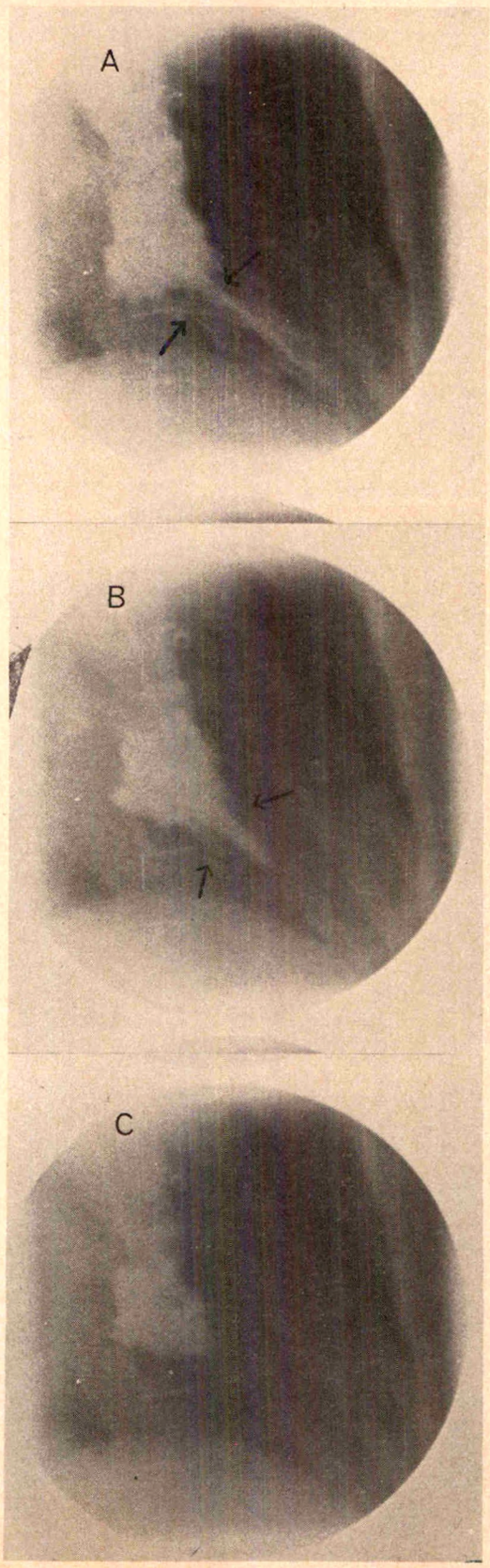


FIGURE 2. Left ventriculogram in the right anterior oblique projection showing the sequence of events during the latter part of systole (**A** to **C**). **Arrows** show papillary muscle hypertrophy. **C** shows obliteration of the apex and mid portion of the left ventricular cavity at end-systole.

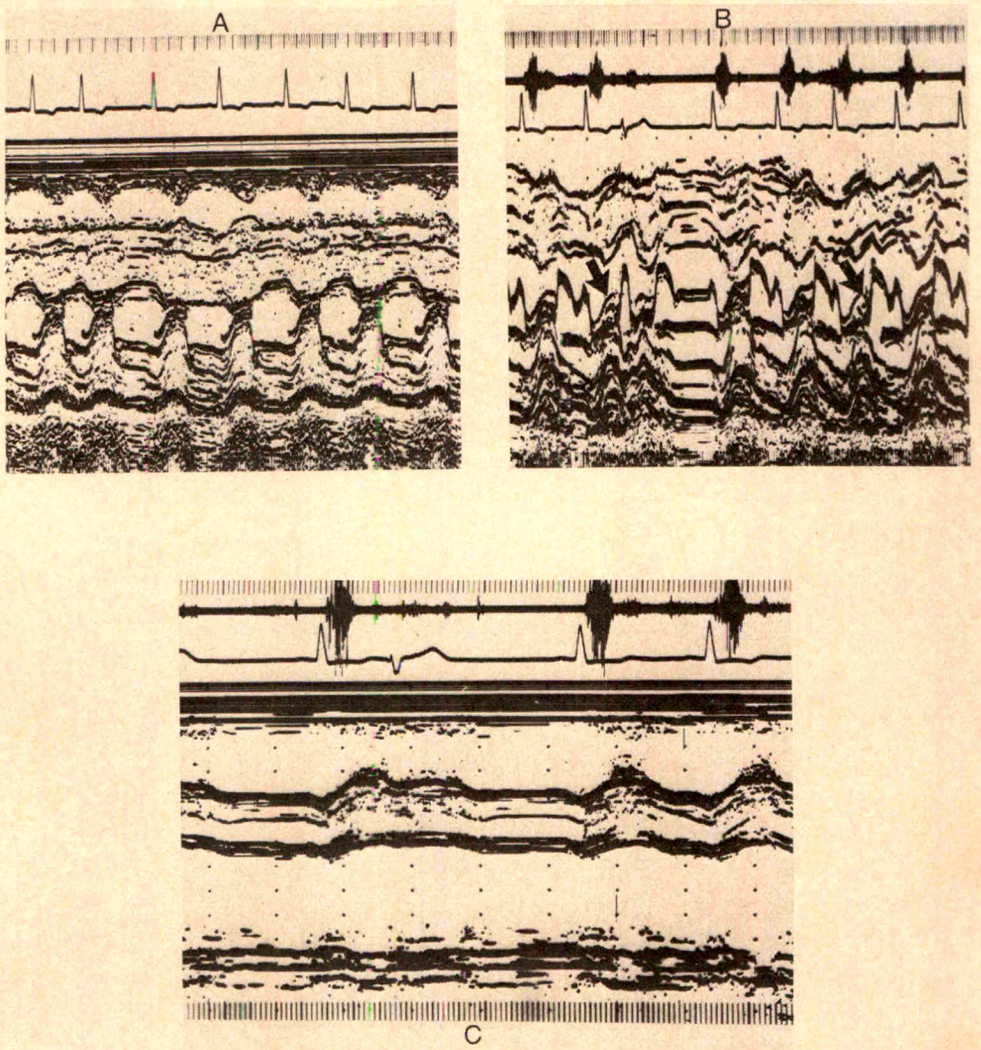


FIGURE 3. Echocardiograms. **A** and **B** show asymmetric septal hypertrophy at the submitral and mitral valve levels, respectively. The **arrows** indicate a small systolic anterior motion of the mitral valve leaflet echoes. **C**, normal echogram from the aortic homograft valve.

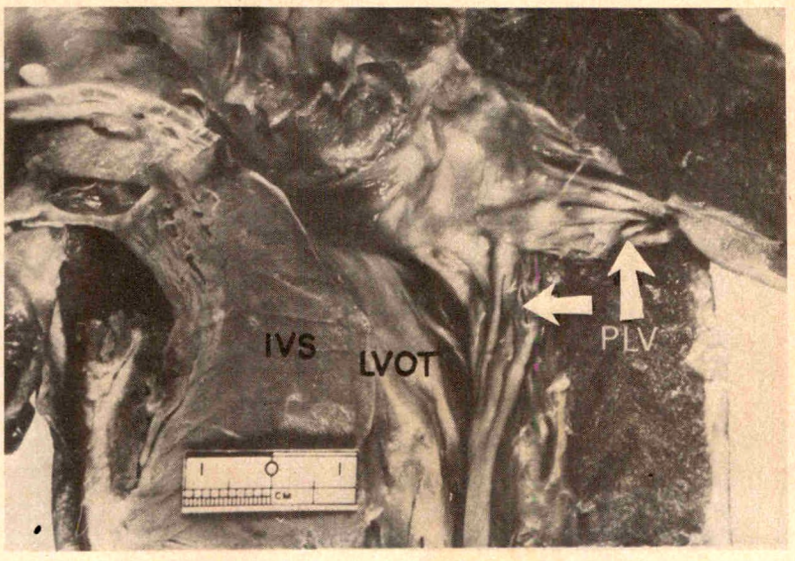


FIGURE 4. Interior view of the left ventricular outflow tract (LVOT) of the heart after fixation in formalin showing asymmetric septal hypertrophy. The upper half of the interventricular septum (IVS) is shown to bulge into the left ventricular outflow tract. **Arrows** show the thickened chordae tendineae of the anterior mitral valve leaflet. PLV = posterior left ventricular wall.

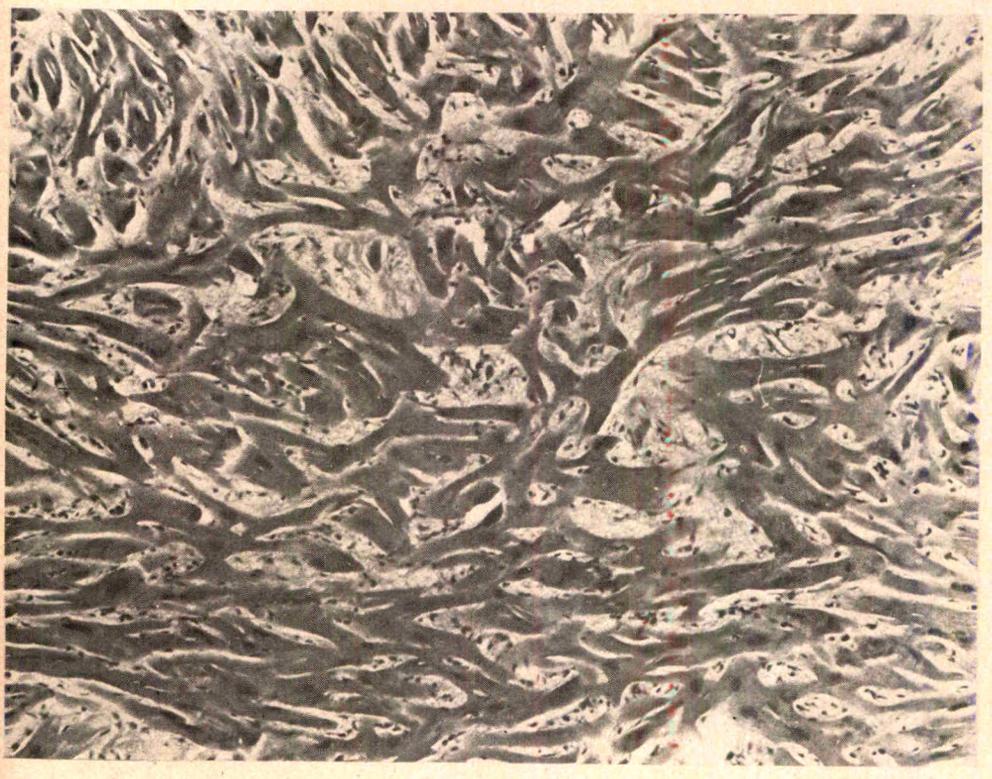


FIGURE 5. Myocardium from the interventricular septum showing disordered arrangement of muscle fibers, which are short and branch abnormally, with some areas showing a whorled pattern. The muscle fibers are generally hypertrophic but vary in thickness, with some appearing degenerate. (Hematoxylin-eosin ×86, reduced by 33 percent.)

were hypertrophied, the largest anterior papillary muscle measuring 1.0 cm across. Focal areas of fibrosis, with no obvious pattern of distribution, were present in the left half of the interventricular septum and the inner half of the left ventricular free wall.

The myocardium of the right ventricle was 0.3 cm thick and measured 2.0 cm below the pulmonary valve. The cavity of this ventricle appeared normal except for the bulging of the interventricular septum already described. The left atrium was not dilated and its myocardium appeared normal. Above the anterior leaflet of the mitral valve was a focal area of endocardial fibrosis that was considered a "jet" lesion. The right atrium appeared normal.

The aortic valve had previously been replaced by a homograft valve that had mildly thickened leaflets. The ascending aorta contained focal scars due to surgical suturing. The origins of the commissures of the original valve could not be discerned.

The mitral valve was abnormal, manifesting fibrous thickening of both the leaflets and the chordae tendineae, but the anterior cusp was more severely affected than the posterior cusp, in which a few chordae appeared to be of normal thickness. A 3 mm flat vegetation was present on the posterior leaflet. This mitral valve appeared to be both stenotic and regurgitant. The tricuspid and pulmonary valves appeared normal.

Microscopic examination: Sections of the myocardium from the interventricular septum showed areas of disordered arrangement of muscle fibers with a characteristic whorled appearance (Fig. 5). The abnormally branching fibers were generally broad and had some atypical nuclei, but other fibers were degenerate with areas of replacement fibrosis. Similar findings were also seen in the left ventricular free wall and the right ventricle, although the fibrosis in the latter ventricle was minimal. The myocardial fibers in the atria were also short and broad. These myocardial changes indicated hypertrophic cardiomyopathy.

Histologic study of the anterior cusp of the mitral valve showed thickening of a nonspecific mechanical type involving both the leaflet and the chordae. Superficial deposition of fibrin was present, occurring as part of a continuing wear and tear process. No inflammation was present in this cusp. Similar changes, but of a lesser degree, were seen in the posterior cusp. The possibility that the mitral valve disease was due to chronic rheumatic disease was initially considered but rejected because there were no histologic features suggestive of this disease. The small vegetation on the posterior cusp was due to fibrin deposition. Superior to the posterior cusp in the atrium was a small area of subendocardial fibrosis, indicating a "jet" lesion. The tricuspid valve showed collagen but was within normal histologic limits as was the pulmonary valve.

Microscopic examination of the aortic wall showed a disordered arrangement of the smooth muscle and elastic tissue (Fig. 6) in the aorta well above the aortic valve in an area where the fiber architecture is normally regularly oriented. The pattern was that described as "higgledy-piggledy."[13]

Ten Relatives

Clinical data: All 10 relatives were asymptomatic and normotensive. The only abnormal physical signs were an ejection click at the left sternal edge in Case I 2 and an ejection systolic murmur at the left sternal edge in Case III 2.

Electrocardiograms: All 10 relatives had sinus rhythm with a normal electric axis. The only abnormalities were minor ST-T changes in Case III 3.

Echocardiograms and phonocardiograms: Echocardiograms revealed asymmetric septal hypertrophy in 4 of the

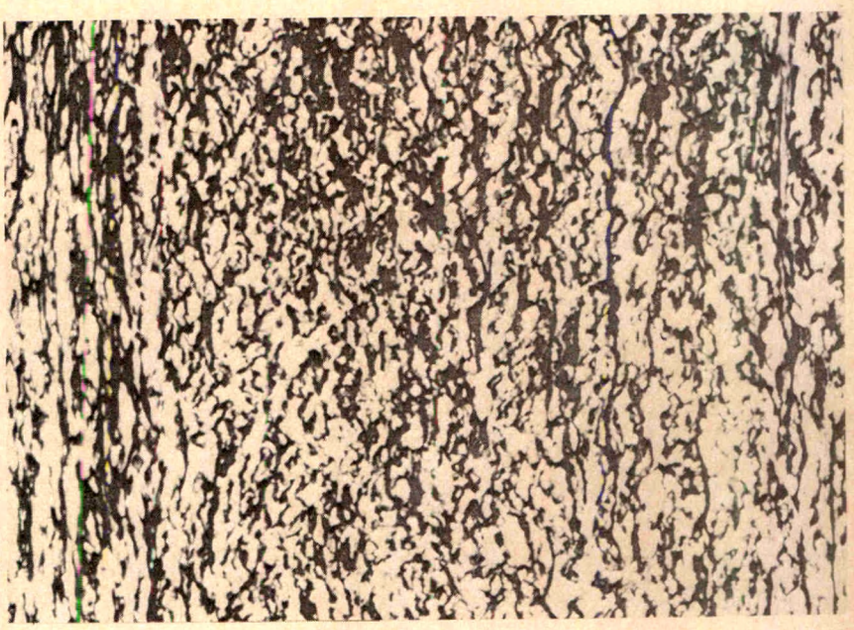


FIGURE 6. High power view of the media of the aorta showing an abnormal elastic fiber arrangement with disorganization and fragmentation of the elastic lamina. The arrangement follows the pattern of the smooth muscle fibers and has been termed "higgledy-piggledy." (Gomeri's stain for elastic tissue ×86, reduced by 30 percent.)

10 relatives, with septal to posterior wall thickness ratios ranging from 1.33 to 1.82 and abnormal aortic eccentric indexes in three relatives ranging from 1.3 to 1.42. Three relatives had coexisting asymmetric septal hypertrophy and an abnormal aortic eccentric index. In addition, the echocardiogram of one subject (Case III 2) revealed forward displacement of the mitral valve leaflet echoes during systole that was considered compatible with the diagnosis of hypertrophic cardiomyopathy.

Phonocardiograms confirmed the clinically detected systolic murmur in Case III 2 and the ejection click in Case I 2, and revealed a clinically unsuspected mid systolic click in Case III 1. Table II presents the detailed echocardiographic data of the four generations and Figure 7 the echocardiographic and phonocardiographic recordings from Cases I 2, III 2 and III 3. Figure 7D shows the subtle aortic valve abnormality.

Discussion

Combined aortic valve stenosis and hypertrophic cardiomyopathy: In recent years it has been recognized that fixed obstruction to the left ventricular outflow tract may coexist with hypertrophic cardiomyopathy.[1–9] This study was undertaken after the classic echocardiographic features of hypertrophic cardiomyopathy were found in a patient who 9 years previously had had an aortic homograft replacement for calcific aortic stenosis thought to be due to a congenital bicuspid valve. This case is of particular interest because the ventricular architecture had not been disturbed by myectomy or myotomy, and there was no significant residual stenosis at the site of the homograft.

TABLE II

Echocardiographic Data on the Family Study (Cases I 1 to IV 4)

Case no.	Age (yr) & Sex	Normal IVS–PLV Thickness (cm) Range	Normal IVS–PLV Thickness (cm) Mean	IVS Thickness (cm)	PLV Thickness (cm)	IVS to PLV Thickness Ratio (Diastolic)	Aortic Valve Eccentricity Index
I 1	75M	0.9–1.1	1.0	1.2	1.0	1.20	1.00
I 2*	74F	0.9–1.1	1.0	2.0	1.1	1.82	1.30
II 1	53M	0.9–1.1	1.0	1.5	1.0	1.50	1.10
II 2	50M	0.9–1.1	1.0	NC	NC	NC	NC
II 3	47F	0.9–1.1	1.0	1.8	1.2	1.50	1.14†
III 1	27F	0.9–1.1	1.0	1.0	1.0	1.0	1.0
III 2‡	26M	0.9–1.1	1.0	NM	NM	NM	1.1
III 3	26M	0.9–1.1	1.0	1.3	0.8	1.63	1.38
IV 1	5F	0.5–0.7	0.6	0.8	0.6	1.33	1.42
IV 2	7M	0.6–0.7	0.7	0.7	0.7	1.0	1.04
IV 3	4F	0.5–0.7	0.6	0.5	0.5	1.00	1.20
IV 4	8M	0.6–0.7	0.7	0.6	0.5	1.20	1.06

* Patient with ejection click.
† Homograft valve.
‡ Patient with systolic anterior motion of the mitral valve and a systolic murmur at the left sternal edge.
IVS = interventricular septum; NC = investigation not carried out; NM = not measurable; PLV = posterior left ventricular wall.

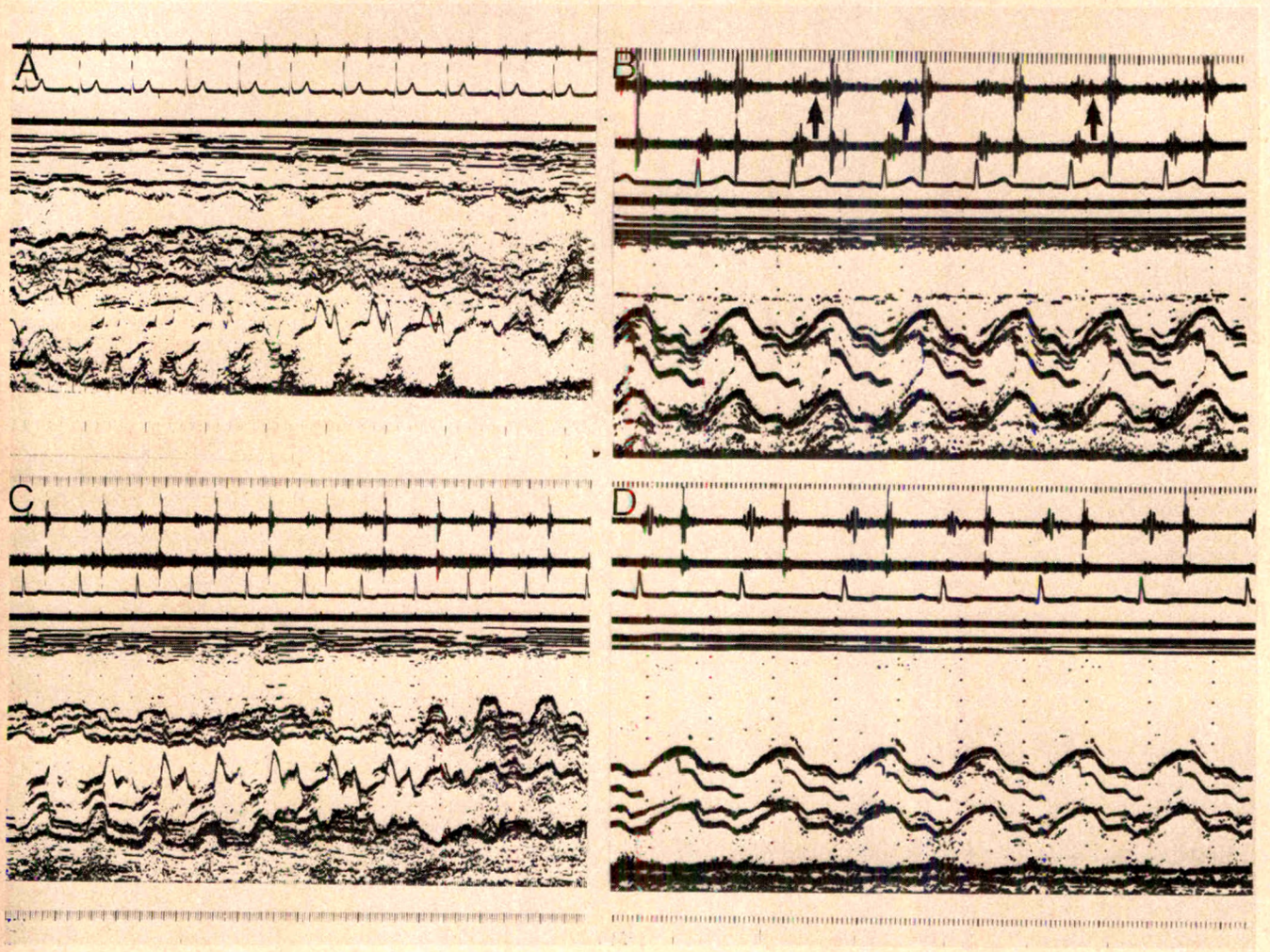


FIGURE 7. Echocardiograms and phonocardiograms of three relatives of the propositus. **A** and **C** show M mode scan of the left ventricle in Cases I 2 and III 3, respectively, and **B** and **D** show the aortic valve echograms in Cases III 2 and III 3, respectively. **A** and **C** reveal asymmetric septal hypertrophy. **Arrows** in **B** indicate the systolic ejection murmur, recorded in the phonocardiogram at the left sternal edge, and **D** reveals eccentric aortic cusp echoes during diastole.

The lack of regression of the left ventricular hypertrophy 9 years after operation was evident clinically, electrocardiographically and hemodynamically. It suggested that the myocardial hypertrophy was probably not solely due to the obstruction at the aortic valve. Further evidence that the hypertrophy was independent of the valve disease was provided by the confirmation of the asymmetric nature of the hypertrophy at autopsy and the finding of histologic changes in the myocardium, consisting of areas of disordered arrangement of broad muscle fibers with atypical nuclei and a whorled pattern indistinguishable from the patterns described in association with hypertrophic cardiomyopathy.[12,14–16] However, some authors still question whether the myocardial histologic findings in hypertrophic cardiomyopathy are pathognomonic for this disease.

The possibility that the aortic valve disease in our patient was due to chronic rheumatic valve disease was considered, particularly in view of the initial operative finding of a small triangular-shaped orifice. However, the pathologic examination at that time suggested a congenital bicuspid valve because the cusps were of different sizes; it was thought that both of the apparent cusps were, in fact, a single cusp with a prominent raphe. No histologic examination was made at that time.

At autopsy 9 years later it was not possible to determine the site of the original aortic valve commissures because of the insertion of the homograft valve. Subsequent supportive evidence for the absence of past rheumatic heart disease was the failure to find signs of residual disease in the heart at autopsy and the finding that the mitral valve thickening was due to mechanical factors.

The significance of the aortic wall changes, consisting of a disordered arrangement of the smooth muscle and elastic tissue, is not known. This type of abnormality has been reported in association with idiopathic cardiomegaly (hereditary cardiovascular dysplasia),[14] arteriosclerosis of infancy,[13] isolated pulmonary valve stenosis[17] and supraaortic stenosis,[18] and the pattern

has been termed "higgledy-piggledy."[13] We are not aware of reports of patients with congenital aortic stenosis who have this abnormal aortic structure, although this combination of conditions was recently observed in a 10 year old girl (Somerville, Becu and Farrer-Brown, 1977). It has been suggested that the "higgledy-piggledy" pattern should be regarded as a healing response to a noxious fetal injury that may be caused by rubella or various chemical, metabolic or genetic factors.[17]

Familial coexistent bicuspid aortic valve and hypertrophic cardiomyopathy: This family study provides additional evidence of the coexistence of bicuspid aortic valve and hypertrophic cardiomyopathy although the abnormalities were rather subtle in some young asymptomatic members. The absence of an ejection click in two relatives (Cases III 3 and IV 1) with an abnormal aortic cusp eccentric index does not rule out congenital bicuspid valve because similar aortic cusp eccentric index measurements without an ejection click were observed in our laboratory in several surgically documented cases of mild aortic stenosis associated with a congenital bicuspid valve. In these instances, the aortic gradient was mainly a subvalve gradient. A false positive indication of bicuspid aortic valve may be obtained from the echocardiograms of patients with a previously damaged tricuspid aortic valve, but there was no history to suggest acquired valve disease in our cases, and the echocardiograms were considered technically acceptable.

These findings may explain the immediate diastolic murmur of aortic regurgitation occasionally seen with hypertrophic cardiomyopathy.[19–21] Among 15 previously described patients with hypertrophic cardiomyopathy,[9] 3 had immediate diastolic murmurs. Reexamination of the aortic valve echocardiograms of these patients revealed eccentric and abnormal separation of the cusp echoes during diastole, compatible with a regurgitant bicuspid valve. It is also possible that a bicuspid aortic valve may be the site of infection that has been reported in hypertrophic cardiomyopathy.[22–24] Furthermore, the coexistence of hypertrophic cardiomyopathy and a bicuspid aortic valve may explain the poor correlation sometimes found between the degree of left ventricular hypertrophy evident in the electrocardiogram and the gradient across the aortic valve.[25–27] When electrocardiographic abnormalities suggest severe left ventricular hypertrophy in the absence of a significant gradient, the disproportionate ventricular hypertrophy may be due to an underlying cardiomyopathy. Occult cardiomyopathy may also be the cause of unexpected deaths in patients with apparently mild aortic valve disease.

Implications: When hypertrophic cardiomyopathy coexists with aortic valve disease, the signs of the former may be obscured until the fixed obstruction has been relieved; however, it is usually possible to detect the presence of both abnormalities before operation with echocardiography and a detailed hemodynamic assessment.

There are also reports of the coexistence of a variety of congenital heart lesions with hypertrophic cardiomyopathy as assessed from hemodynamic, angiographic and anatomic criteria.[2,9,28–33] Recently, the typical histologic changes of hypertrophic cardiomyopathy as well as the "higgledy-piggledy" pattern in the aortic wall have been reported in association with isolated pulmonary valve stenosis.[17]

This study supports the view that hypertrophic cardiomyopathy may not be an abnormality confined to the myocardium but may also affect other parts of the cardiovascular system. Examination of the first degree relatives of our patient provided further evidence of the coexistence of hypertrophic cardiomyopathy and bicuspid aortic valve. The combined entity appeared to have a pattern of dominant inheritance with variable clinical expression.

Addendum

During the preparation of this paper one of us (Ö.F.) observed the echocardiographic and myocardial histologic features of hypertrophic cardiomyopathy in two further patients with congenital aortic valve disease. The coexistence of these two conditions may be more common than hitherto thought.

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Myocardial Biopsy: A Useful Diagnostic Procedure or Only a Research Tool?*

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In 1962, Sakakibara and Konno[1] reported doing endomyocardial biopsies in patients using a catheter inserted into the right ventricle from a systemic vein. The right ventricular aspect of the ventricular septum was the portion of heart biopsied. Biopsy specimens of human left ventricular wall were obtained as early as 1956[2] with use of a transthoracic needle (using methods similar to those employed in a hepatic biopsy) and later by various modifications of the Konno catheter.[3–9] The report by Mason[10] in this issue of the Journal describes still another method of biopsy of the myocardium performed with a catheter and mentions that 1,300 cardiac biopsies have been performed in recent years by one or more catheter techniques in a single institution. It is now recognized that closed chest cardiac biopsy can be performed with a catheter at minimal risk and that several specimens can be obtained for examination during the same procedure. This editorial will attempt to summarize what has been learned to date from myocardial biopsies obtained by these closed chest catheter methods and to ask if the procedure is worth the risk, time and expense.

Since 1968, we have studied in our laboratory approximately 90 endomyocardial biopsy specimens, two thirds obtained with the Konno or the Olympus catheter from the right ventricle and one third with transthoracic Menghini needle biopsy of the left ventricular wall.[11] Most of these specimens were from patients who had some type of cardiomyopathy. The Konno catheter biopsies were performed by Drs. Rashid A. Massumi and Nayab Ali,[3,8] and the needle biopsies by Dr. Gerald I. Shugoll.[12] In addition, we have examined operatively obtained biopsy tissue from either the left or the right ventricle or the left atrium from more than 100 patients with various types of congenital and acquired heart diseases.[13–19] All biopsy samples were studied histologically; most were also studied with transmission electron microscopy and some were also studied histochemically. What was learned from these studies and from those of others?

1. Many details of the subcell pathology of human hearts were learned by study of the closed chest biopsy specimens. Similar observations were made, however, on cardiac biopsy tissue obtained from patients undergoing various types of cardiac operations, primarily open heart procedures. Thus, much of the "cell biology" type of information (as opposed to purely diagnostic information) derived from the closed chest biopsies also was obtained, often with fewer artifacts, at open chest biopsy.

2. The endomyocardial biopsies have had limited value from a diagnostic standpoint.

Idiopathic dilated cardiomyopathy: The biopsies provided the first opportunity to study ultrastructurally well preserved myocardium in patients with this condition.[20] Earlier ultrastructural studies[21] had been limited to tissues obtained at necropsy that showed considerable autolytic changes. The biopsies allowed documentation of the extent of the myocardial damage present but failed to disclose specific histologic or ultrastructural features that could be used as qualitative "markers" to establish the diagnosis of this condition. Thus, the diagnosis of idiopathic dilated cardiomyopathy cannot be made on the basis of myocardial biopsy, although there is generally a good correlation between the severity of the condition clinically and the extent of the morphologic changes.[11,22]

Especially disappointing have been the failures of biopsy studies to find viral particles or specific histochemical or immunohistochemical "markers" in the myocardium of patients with idiopathic dilated cardiomyopathy. Similarly, viral culture studies of myo-

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cardial biopsy material from patients with idiopathic dilated cardiomyopathy appear to have met with little success. Although myocardial biopsies are potentially useful for biochemical studies, surprisingly little work has been published on this subject. The small size of the biopsy specimens severely limits the performance of many biochemical procedures, particularly those requiring extensive preparatory steps (such as cell fractionation). Nevertheless, a combined biochemical and ultrastructural study of tissue obtained by operative biopsy showed that cardiac muscle myosin from patients with hypertrophic cardiomyopathy does not differ from normal in its adenine triphosphatase activity, in its ability to form bipolar rods or in the morphologic features of such rods.[23]

Myocardial tissues from patients with idiopathic dilated cardiomyopathy appear to differ morphologically from those of patients with other types of heart disease quantitatively (that is, the extent of the hypertrophy and the damage) rather than qualitatively. Such differences must be evaluated in relation not only to the nature, but also to the severity and duration of the basic disease processes. Quantitative analysis (morphometry), including changes in surface/volume ratios and in the percent of cell volume occupied by myofibrils, mitochondria, nuclei and other organelles, presents a new approach to the study of cardiac ultrastructural alterations.[24,25] It is uncertain whether this methodology will have diagnostic applications, although it has become clear that morphometric analysis can detect various structural changes that are not recognizable from simple visual study of electron micrographs. Nevertheless, morphometric study presents formidable technical and statistical problems. It is only in the last few years that progress has been made in this area of cardiac pathology, and most of this progress has been in studies of relatively early and uncomplicated hypertrophy in small experimental animals.[24,25] The tissue fixation requirements considered necessary for such studies are extremely strict (including fixation by vascular perfusion) in order to minimize data scatter (that is, inhomogeneity in tissue structure) resulting from regional differences in the quality of the fixation. These requirements increase the practical difficulty of morphometric studies based on biopsy material, in which the tissue sample is small and often shows appreciable artifactual ultrastructural changes. These changes are due to tearing of tissue by the cutting edges of the biopsy instrument and to the unopposed contraction (leading to formation of hypercontraction bands and to translocation of cell organelles) of cells at the edges of the biopsy specimen. In fact, these changes can mimic true pathologic changes and can be the source of considerable difficulty in the qualitative evaluation of myocardial biopsy specimens.[11] An empirical answer has not yet been given to the complex question of how representative a biopsy sample (or two or three) is of the state of the whole heart. Obviously, the answer will depend not only on the exact site of the biopsy (right side of ventricular septum versus left ventricular free wall) but also on the focal or diffuse nature of the changes occurring in a given disease. Brooksby et al.[4] reported that the microscopic appearance of left and right ventricular biopsy specimens differed in 60 percent of their patients.

Idiopathic hypertrophic cardiomyopathy: The closed chest myocardial biopsy samples are of inadequate size to establish firmly the diagnosis of hypertrophic cardiomyopathy with this method. Nevertheless, the cardiac biopsy specimens obtained at open thoracotomy (at the time of the therapeutic cardiac operation) have provided much detailed ultrastructural information about myocardial cells in this condition.[26,27] The closed chest biopsy specimens are usually too small to evaluate disarray of groups of cells, but they have provided information about disarray of myofibrils and myofilaments within individual myocytes. A striking demonstration of these changes has been provided by a recent scanning electron microscopic study.[28] Most of the ultrastructural information on myocardium in patients with hypertrophic cardiomyopathy, however, has been obtained by study of either biopsy specimens or resected tissue obtained at open thoracotomy. Furthermore, it is now known that the foci of disarray of whole cells and of their contractile elements do not constitute a specific "marker" for the diagnosis of hypertrophic cardiomyopathy. Such changes also occur (although usually to a smaller extent than in hypertrophic cardiomyopathy) in certain patients with other types of heart diseases (see Ref 29 for review). Thus, additional ultrastructural information to be provided by closed chest endomyocardial biopsy in hypertrophic cardiomyopathy appears limited.

Infiltrative cardiomyopathies: Of the various types of cardiomyopathy, endomyocardial biopsy is most likely to be useful from a diagnostic standpoint in the infiltrative group. In the patient with cardiac dysfunction due to cardiac *amyloidosis*, the amyloid deposits are extensive throughout the ventricular wall and, therefore, myocardial biopsy studies are likely to be positive if the cardiac dysfunction is on the basis of cardiac amyloidosis. In amyloidosis involving the heart,[30] however, other organs usually contain amyloid deposits and, thus, biopsy studies of the tongue, liver, rectum, skin and other areas are also likely to be positive, and these tissues are more accessible to biopsy than is the heart. The same can be said for cardiac *hemosiderosis*.[31] When there is enough iron in the heart to cause it to function abnormally, iron deposits always are present in virtually every other body organ.[31] The same is true of the glycogen deposits in types II, III and IV *glycogen storage disease*.[32] *Granulomatous myocarditis*, which generally means *sarcoidosis*, is a focal process in the heart, in contrast to disease due to amyloid, iron or glycogen.[33] Thus, biopsy findings could be negative when many granulomas actually are present in the myocardium. Granulomas in sarcoidosis tend to involve preferentially the ventricular septum; therefore, biopsy may be worthwhile if this condition cannot be diagnosed by another means.[33]

Drug-induced cardiomyopathy: Endomyocardial biopsy studies in patients with *adriamycin cardiomy-*

opathy have proved informative by documenting damage to various myofiber organelles, but they have been less useful in predicting in which patients adriamycin cardiomyopathy will develop.[34]

Similarly, various myocardial changes have been documented by biopsy studies in patients with certain *congenital cardiomyopathies*,[35] but again the changes have not been useful diagnostically.

Cardiac transplants: In patients with cardiac transplantation the Stanford group[36] has demonstrated that endomyocardial biopsy is useful in diagnosing transplant rejection and in evaluating therapeutic intervention to counteract it. Thus, for this limited group of patients, endomyocardial biopsy appears useful from a diagnostic standpoint.

In summary, closed chest endomyocardial biopsy in the more common varieties of cardiomyopathy—the dilated and hypertrophic types—has been informative but rarely diagnostic. In the uncommon varieties of cardiomyopathy—amyloid, iron, glycogen, granuloma, neoplasm—this procedure is more useful from a diagnostic standpoint, but diagnosis of these disorders usually can be established more readily by biopsy of another more easily accessible tissue or organ.

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The Heart Patient Recovers, by Sydney H. Croog, PhD and Sol Levine, PhD. New York, New York, Human Sciences Press, 1977, 432 pages, $9.95

Hypertension Mechanisms, Diagnosis & Management, edited by James O. Davis, MD, John H. Laragh, MD and Amy Selvyn. New York, New York, HP Publishing, 1977, 274 pages

Infective Endocarditis, edited by Shahbudin H. Rahimtoola, MD. New York, Grune & Stratton, 1977, 386 pages, $31.50

The Marathon: Physiological, Medical, Epidemiological, and Psychological Studies, edited by Paul Milvy. New York, New York Academy of Sciences, 1977, 1090 pages, $75.00

Mechanical Concepts in Cardiovascular and Pulmonary Physiology, by Jerry Franklin Green, PhD. Philadelphia, Lea & Febiger, 1977, 166 pages, $10.00

Medical Information Systems. A Resource for Hospitals, by Melville H. Hodge. Germantown, Maryland, Aspen Systems, 1977, 201 pages

Modern Cardiology, by John D. Cantwell, MD, Woburn, Massachusetts, Butterworths Publishers, 1977, 468 pages, $24.95

Pathology of Ischaemic Heart Disease, by Theo Crawford, MD. Woburn, Massachusetts, Butterworths, 1977, 170 pages, $21.95

Pheochromocytoma, by William Muir Manger and Ray W. Gifford, Jr. New York, Heidelberg, Berlin, Springer-Verlag, 1977, 398 pages, $49.80

Principles of Cardiac Arrhythmias, second edition, by Edward K. Chung, MD. Baltimore, Maryland, Williams & Wilkins, 1977, 770 pages, $49.50

Progress in Cardiology, edited by Paul N. Yu, MD, and John F. Goodwin, MD. Philadelphia, Pennsylvania, Lea & Febiger, 1977, 211 pages

Psychosocial Care of the Dying Patient, edited by Charles A. Garfield. New York, McGraw-Hill, 1978, 430 pages

Respiratory Intensive Care, edited by Robert M. Rogers, MD. Springfield, Illinois, Charles C Thomas, 1977, 425 pages, $29.50

Self-Assessment in Electrocardiography, by Stelio Mangiola, MD. Philadelphia, J. B. Lippincott, 1977, 205 pages, $15.00

Treatment of Cardiac Emergencies, second edition, by Emanuel Goldberger, MD and Myron W. Wheat, Jr., MD. St. Louis, Missouri, C. V. Mosby, 1977, 391 pages, $16.50

Vascular Grafts, edited by Philip N. Sawyer and Martin J. Kaplitt. New York, Appleton-Century-Crofts, 1978, 432 pages, $38.75

RESEARCH TRAINING PROGRAMS

The need for fully trained independent investigators and teachers continues to be a matter of great concern to the Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute. Approximately one fourth the number required to meet conservatively estimated needs are currently in training.

In order to increase current support levels, the Division of Heart and Vascular Diseases is vigorously encouraging research training programs. Individual Postdoctoral Fellowships are available to support research training of cardiovascular investigators in a variety of disciplines to promote multidisciplinary research capability. The research training may be in fundamental studies of basic processes and functions or clinical investigations. They may involve behavioral studies, including risk factor modification (e.g., diet, smoking), genetics (including studies of populations) and primary or secondary prevention. They should aim toward long-term involvement in research toward increasing knowledge and understanding in cardiovascular areas. Fundamental studies are considered highly relevant to programs in Hypertension, Arteriosclerosis, Coronary Heart Disease, Cardiovascular Aspects of Diabetes, Arrhythmias, Heart Failure and Shock, Cerebrovascular Disease, Peripheral Vascular Disease, Congenital and Rheumatic Heart Diseases, Cardiomyopathies and Infections of the Heart, Circulatory Assistance, and Cardiovascular Devices and Technology. Support of training only to acquire or improve clinical abilities is precluded under this Research Fellowship Program.

Individual Postdoctoral Fellowships are available to recipients of a doctoral degree who are United States citizens or non-citizens who have been admitted for permanent residence. Research training should be in the above or other disciplines related to heart and vascular diseases or fundamental cardiovascular processes. Applicants must be sponsored by an investigator at a domestic or foreign nonprofit public institution that has the staff and facilities to provide the desired training. Applications for training outside the United States require a detailed justification of the need to study abroad based on the unique facilities and/or training opportunities. Stipends range between $10,000 and $13,200 for the first year of postdoctoral research training depending on the years of relevant postdoctoral experience, and may be supplemented from non-Federal funds. Usual payback activity requires research or teaching for a period equal to the duration of training support. Alternative payback requires 20 months service for each 12 months of training support.

Deadlines for the receipt of applications are:

June 1 with announcement of results in February

October 1 with announcement of results in May

Further information or applications may be obtained from: Dr. Max A. Heinrich, Jr., Manpower Branch, Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20014. Telephone: (301) 496-1724.

Five Finalists' Abstracts: Young Investigators' Awards Competition American College of Cardiology, 27th Annual Scientific Session Anaheim, California, March 6 to 9, 1978

Winner ($1,000 Award)

ALPHA-ADRENERGIC RECEPTORS IN RAT MYOCARDIUM: DIRECT IDENTIFICATION BY BINDING OF [^{3}H]DIHYDROERGOCRYPTINE

R. Sanders Williams, M.D. and Robert J. Lefkowitz, M.D.
Duke University Medical Center, Durham, N.C.

[^{3}H]Dihydroergocryptine ([^{3}H]DHE) binds to sites in membranes derived from rat myocardium that have the characteristics expected of physiologic alpha-adrenergic receptors. The binding is saturable with 41 fmol [^{3}H]DHE bound per mg. protein and of high affinity with K_D= 2.9 nM. The binding is rapid and readily reversible. Adrenergic agonists compete for binding of [^{3}H]DHE in the order: epinephrine> norepinephrine>> isoproterenol; and adrenergic antagonists compete for binding in the order: phentolamine>>propranolol. For comparison, (-)[^{3}H]dihydroalprenolol ((-)[^{3}H]DHA) was used to bind to sites in the same membrane preparations having characteristics indistinguishable from physiologic beta-receptors. The number and affinity of beta-receptors were quite similar to the alpha-receptors with 46 fmol (-)[^{3}H]DHA per mg. protein bound at saturation and K_D= 2.5 nM. These techniques allowed identification of both beta and alpha-adrenergic receptors in membranes derived from isolated atria, right ventricular free walls, and left ventricles including interventricular septae. This is the first report documenting direct identification of myocardial alpha-receptors by radioligand binding techniques and complements the literature previously reporting myocardial inotropic and electrophysiologic responses to alpha-adrenergic stimulation.

Second Place ($250 Award)

OBSERVATIONS UPON THE CONCEPT OF "CRITICAL" CORONARY STENOSIS.

Robert L. Feldman, MD; Wilmer W. Nichols, Ph.D; Carl J. Pepine, MD, FACC; Donald A. Conetta, MD; C. Richard Conti, MD, FACC. University of Florida, Gainesville, Fla.

Although considerable investigation has been devoted to the concept of "critical" coronary stenosis, there is general lack of agreement on which coronary stenoses consistently decrease coronary blood flow (CBF). In 30 open chest dogs we studied CBF and the aorto-distal coronary pressure gradient at rest and with reactive hyperemia (RH) as different stenoses were created. Short calibrated snare stenoses on the left coronary artery (LCA) or its major branches, anterior descending (LAD) and circumflex (LCx), were used to assess the effect of the location of lumen diameter reduction. In other experiments diameter reduction was held constant and the stenosis length was progressively increased from 1 to 15 mm. In a third group of studies series of multiple 1 mm long stenoses were created. The accuracy and constancy of diameter reduction was confirmed with in vivo coronary angiography and post mortem polysulphide casts.

Short snare stenoses of greater than 80% diameter reduction were necessary to affect resting CBF or distal coronary pressure of the LCA or either major branch. Lengthening 50-60% LAD or LCx stenoses beyond 5 mm caused similar effects. Series of two or three 1 mm stenoses did not decrease CBF but slightly increased the pressure gradient. During RH a 60% LCA or branch snare stenosis decreased peak CBF responses. With LAD or LCx stenosis peak RH CBF responses decreased further as length increased. Multiple stenoses affected peak RH CBF responses significantly more than continuous stenoses.

These data indicate that important variables related to coronary stenosis include (1) diameter reduction, (2) length and (3) number.

Honorable Mention ($100 Award)

REGIONAL MECHANICAL PERFORMANCE WITH POSTEXTRASYSTOLIC POTENTIATION, EPICARDIAL ELECTROGRAM, REGIONAL MYOCARDIAL BLOOD FLOW AND INFARCT SIZE DURING PROLONGED ISCHEMIA

William E. Boden, MD; Chang-seng Liang, MD, PhD; and William B. Hood, Jr., MD, FACC; Thorndike Memorial Laboratories, and Boston Univ. Sch. of Med., Boston, Mass.

Postextrasystolic potentiation (PESP) is an effective means of defining myocardial contractile reserve during ischemia (I). We systematically employed PESP in evaluating myocardial contractile performance in 14 open-chest dogs subjected to 4 hr I, followed by 1 hr of reperfusion (R). The intrinsic regional contraction patterns in central ischemic (IZ), border (BZ) and control zones (CZ), during right ventricular pacing (134±2 beats/min) were compared to PESP responses following single, closely-coupled (179±3 msec) extrasystoles, during I and R. Pressure-length loop areas (mm Hg-cm), an index of segmental work, were compared to other indices of ischemic injury: ST segment elevation (ST↑), regional myocardial blood flow (MBF) and size of infarct (SI, % necrosis of the transmural segment) using tetrazolium blue. The results (mean±SE; *$p<0.05$ before/after PESP) are:

	Control	30 min I	1 hr I	4 hr I	30 min R	1 hr R
CZ	11±1	8±2	8±2	8±2	9±2	9±2
CZ+PESP	17±2*	15±2*	16±2*	16±2*	16±2*	15±2*
BZ	12±2	3±2	3±2	2±2	4±1	4±1
BZ+PESP	19±2*	15±2*	14±2*	12±1*	13±1*	13±1*
IZ	11±1	-13±3	-11±3	-11±3	-6±2	-2±2
IZ+PESP	16±2*	-6±3*	-5±3*	-6±3*	-1±2*	-1±2

At 4 hr I, ST↑ was 2.0 mV in BZ and 10.0 mV in IZ; MBF decreased 52% to 60 ml/min/100g in BZ and 78% to 28 ml/min/100g in IZ. SI was 55±10% in BZ and 74±7% in IZ. We conclude: 1) PESP enhances both BZ and IZ mechanical performance throughout prolonged I. 2) R improves both BZ and IZ segment work irrespective of PESP. 3) Despite profound abnormalities in MBF, ST↑ and SI, PESP is capable of identifying contractile reserve up to 4 hr I.

Honorable Mention ($100 Award)

INHIBITION OF ADRENERGIC NEUROTRANSMISSION IN ISCHEMIC REGIONS OF THE CANINE LEFT VENTRICLE.

James B. Martins, MD, Affiliate, Richard E. Kerber, MD, FACC, Melvin L. Marcus, MD, FACC, Donald E. Laughlin, MSEE, Donald M. Levy, PhD, CV Cent, Depts of Int Med and Engineering, Univ of Iowa Hosp, Iowa City, Iowa

The purpose of this study was to evaluate functional responses of ischemic myocardium to neurotransmitter released from cardiac sympathetic nerves compared to exogenous norepinephrine. The anterior descending coronary artery was occluded in 8 open-chest dogs and the posterior descending was occluded in an additional 5. Myocardial blood flow was measured with 8 μ spheres. Functional myocardial response was recorded with intramyocardial sonomicrometers which measured segment shortening (+ΔL) in normal regions and expansion (-ΔL) in ischemic regions. Left sympathetic nerve stimulation (LSS) produced equivalent improvement in +ΔL of all regions studied before coronary occlusion. Thirty minutes after occlusion, increases in blood pressure and heart rate during LSS were matched by exogenous NE (0.2-0.4 μg/kg/min) administered during atrial pacing. This resulted in similar improvement in +ΔL of normal regions with LSS and NE. After coronary occlusion blood flow in ischemic regions fell to approximately one third of normal and did not improve with either LSS or NE. Despite diminished blood flow exogenous NE improved function of the ischemic anterior wall by decreasing systolic expansion: -ΔL from -0.6±.1(SEM) to -0.3±.1* mm (*=$p<0.025$) while expansion was unchanged during LSS: -ΔL from -0.5±.1 to -0.5±.2 mm. Similar changes were seen with posterior ischemia. While

NE caused significant improvement in function of ischemic myocardium, LSS did not. These results suggest that adrenergic neurotransmitter release was impaired early in regions of myocardial ischemia. This impairment was independent of regional variations in sympathetic innervation.

Honorable Mention ($100 Award)

EVOLUTION OF MYOCARDIAL ABNORMALITIES IN CHRONIC ALCOHOLISM

George Thomas, MD, College of Medicine and Dentistry of New Jersey-New Jersey Medical School, Newark, NJ.

To determine whether the altered left ventricular compliance and indices of contractility in chronic ethanolism are time dependent, a study was undertaken in young healthy male mongrel dogs. Ethanol was fed up to 36% of total daily calories for an average of 18 mos (Group I) or 52 mos (Group II). The short and long-term groups were fed the same diet and given vitamin supplements. The control (N=8) and alcoholic groups (N=8) maintained body weight, hematocrit, plasma vitamins and albumin levels. Left ventricular function was assessed in the intact anesthetized dog using thermodilution for end-diastolic volume and stroke volume determinations. During preload increments with saline infusion, a significantly higher rise of end-diastolic pressure was observed in the ethanol group as compared to the controls, associated with reduced end-diastolic and stroke volume. However, the responses were similar in short and long-term alcoholic animals. Estimation of the collagen in the left ventricle revealed significantly increased collagen accumulation in the myocardium of alcoholic animals, as a basis for the compliance abnormality. Collagen was located in the interstitium by morphologic study and did not vary with duration. An index of left ventricular contractility employing dP/dt normalized for preload and afterload was significantly reduced, as was Vce, only in the long-term animals. Myocardial cation and water distribution was significantly abnormal only in the long-term alcoholic. Cell accumulation of Na^+ and H_2O may limit access of calcium to myofibrils or result in fibril disorientation.

LEARNING CENTER: PROGRAM CALENDAR

The American College of Cardiology's newest department, the Learning Center, located at the College's Bethesda, Maryland headquarters, began operations last October with the offering of its first continuing medical education program for physicians with a specialty or an interest in cardiovascular medicine. The purpose of the Learning Center is to support the professional commitment to quality patient care by providing a new standard of excellence in cardiovascular continuing education.

Each continuing education program is directed toward a specific target group including: adult cardiologists (CD), internists (IM), pediatric cardiologists (PDC), and family practitioners (FP). For additional information concerning the programs listed below or for a complete schedule of programs through October 1978, contact Program Coordinator, Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014 (301) 897-5400.

MAY THROUGH OCTOBER 1978

May 8–10 & May 22–24 **Electrocardiography of Arrhythmias (CD) (IM).** Charles Fisch, MD, FACC, director

May 15–18 & August 7–10 **Update in Cardiology (CD) (IM).** R. Joe Noble, MD, FACC, director

May 31–June 2 **Diagnosis & Management of Clinically Important Arrhythmias (FP) (GP) (IM).** William P. Nelson, MD, FACC, director

June 19–22 **Congestive Heart Failure: A Changing Scene (CD) (IM).** Charles B. Mullins, MD, FACC, director

June 12–14 & October 7–10 **Ubiquitous PVCs: Sorting Out the Dilemma (CD) (IM).** Douglas P. Zipes, MD, FACC, director

CALENDAR OF EXTRAMURAL PROGRAMS

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Extramural Programs Department, Division of Continuing Education, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

MAY 1978 THROUGH OCTOBER 1978

To be arranged individually — **Preceptorships in Cardiology.** Arthur Selzer, FACC, director, Pacific Medical Center, San Francisco, CA

MAY 8–11 — **The Physiologic Basis for Diagnosis and Treatment of the Patient With Heart Disease—A Tribute to William Harvey on his 400th Birthday (1578–1657).** J. Willis Hurst, FACC, director and Robert C. Schlant, FACC, co-director. Colony Square Hotel, Atlanta, GA

MAY 12–14 — **Rational Drug Therapy in Ischemic Heart Disease.** Robert J. Lee, director, Palmer House, Chicago, IL

MAY 12–15 — **A Symposium on Cardiovascular Nursing.** Henry J. L. Marriott, FACC and Leo Schamroth, FACC, directors. Sheraton Sand Key Hotel, Clearwater Beach, FL

MAY 18–20 — **Cardiovascular Nuclear Medicine and Comparative Techniques: 1978.** Lawrence S. Cohen, FACC, Alexander Gottschalk, Barry L. Zaret, FACC, directors. Yale University School of Medicine, New Haven, CT

JUNE 15–17 — **Echocardiography: Fundamentals and New Developments in Cardiac Ultrasound.** Arthur D. Hagan, FACC, director and Walter V. R. Vieweg, FACC and Joel S. Karliner, FACC, co-directors. Sheraton Harbor Island Hotel, San Diego, CA

Aug. 26–28 — **Tutorials in the Tetons: Cardiac Emergencies (Fourth Annual).** Robert S. Eliot, FACC, director and Alan D. Forker, FACC, William P. Nelson, FACC and Gerald L. Wolf, co-directors. Jackson Lake Lodge, Moran, WY

SEPT. 11–14 — **Electrocardiography: Core Curriculum and Self-Assessment.** Paul L. McHenry, FACC, director and Charles Fisch, FACC, co-director. Myers Auditorium, Wishard Memorial Hospital, Indiana University Medical Center, Indianapolis, IN

SEPT. 11–14 — **Electrocardiography: Core Curriculum and Self-Assessment.** Arthur Selzer, FACC, director. Golden Gateway Holiday Inn, San Francisco, CA

SEPT. 14–16 — **The Clinical Pharmacology of Cardiovascular Drugs.** William B. Abrams, FACC, Albert N. Brest, FACC, Richard O. Davies, FACC and R. F. Ferguson, co-directors. Marriott Motor Hotel, Philadelphia, PA

SEPT. 27–29 — **Advanced Echocardiography.** Harvey Feigenbaum, FACC, director and Betty C. Corya, James C. Dillon, FACC and Arthur E. Weyman, FACC, co-directors. Indianapolis Hilton Hotel, Indianapolis, IN

OCT. 12–14 — **Practical Cardiology 1978.** William W. Parmley, FACC and Kanu Chatterjee, FACC, directors. Del Monte Hyatt House, Monterey, CA

OCT. 13–14 — **Geriatric Cardiology.** Raymond Harris, FACC and Borys Surawicz, FACC, directors. Hyatt Regency Hotel, Lexington, KY

OCT. 18–20 — **Cardiac Pacing.** Doris J. W. Escher, FACC and Seymour Furman, FACC, directors. Waldorf-Astoria Hotel, New York, NY

OCT. 18–22 — **Valvular Disease—Practical Diagnosis and Management.** Peter C. Gazes, FACC, director and Charles P. Summerall III, FACC, Grady H. Hendrix, FACC, William H. Barnwell II, FACC, Bruce W. Usher, FACC, J. Lindsay Leviner, Jr. and Robert G. Irvin, co-directors. Kiawah Island, Charleston, SC

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This membership category is open to all Fellows in cardiovascular (adult, pediatric, surgical, etc.) training programs. Upon completion of training and in order to maintain an affiliation with the College, the members are encouraged to apply to the Credentials Committee for status in one of the other three membership categories.

The application for Affiliate (in Cardiovascular Related Training) must be signed by the Director of the applicant's training program and two sponsors, both of whom must be Fellows of the College. One of the sponsors may be the Director of the training program, provided he is a Fellow of the College. The annual dues for an Affiliate (in Cardiovascular Related Training) are $20.00 (U.S.).

Advantages to the Affiliate (in Cardiovascular Related Training)

1. Subscription to *The American Journal of Cardiology,* the official journal of the College.
2. Reduced fees for all educational programs of the College.
3. Preference for enrollment in programs sponsored by the College with a limited registration.
4. Receipt of the quarterly publication, *Cardiology,* the newsletter of the College.
5. Participation in all affairs of the College as a member rather than as a guest of the College.

Those desiring an application form should write to Ms. Margaret E. Coffey, Director, Membership Department, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

28th ANNUAL SCIENTIFIC SESSION
AMERICAN COLLEGE OF CARDIOLOGY.

MARCH 11–15, 1979 MIAMI BEACH, FLORIDA

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The editors of THE AMERICAN JOURNAL OF CARDIOLOGY welcome concise articles devoted to cardiovascular disease. Articles must be contributed solely to THE AMERICAN JOURNAL OF CARDIOLOGY and become the property of the Publisher. The Publisher reserves copyright and renewal on all published material, and such material may not be reproduced in any form without the written permission of the Publisher. Statements in articles are the responsibility of the authors. Authors will assist the editors in the prompt processing of manuscripts if these instructions are followed:

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- Address manuscript to Managing Editor, American Journal of Cardiology, 666 Fifth Ave., New York, NY 10019.
- Submit two copies of all elements of the article: text, references, legends, tables and figures.
- Arrange the paper in this order: (1) title page; (2) abstract; (3) text; (4) references; (5) legends; (6) tables; and (7) figures.
- Number all pages in above sequence, beginning with title page as 1, abstract as 2, etc.
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- Cite in numerical order every reference, figure and table. (Order of mention in text determines the number given to each.)
- Place acknowledgments at end of text, before references.

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31. Vismara LA, Vera Z, Miller RR, Mason DT: Efficacy of disopyramide phosphate in the treatment of refractory ventricular tachycardia. Am J Cardiol 39:1027–1034, 1977

(Author: please note that no periods are used after authors' initials.)

For books (edited by other than author of article):

28. Schiebler GL, Van Mierop LHS, Krovetz LJ: Diseases of the tricuspid valve, chap 20. In, Heart Disease in Infants, Children and Adolescents (Moss AJ, Adams F, ed). Baltimore, Williams & Wilkins, 1968, p 134

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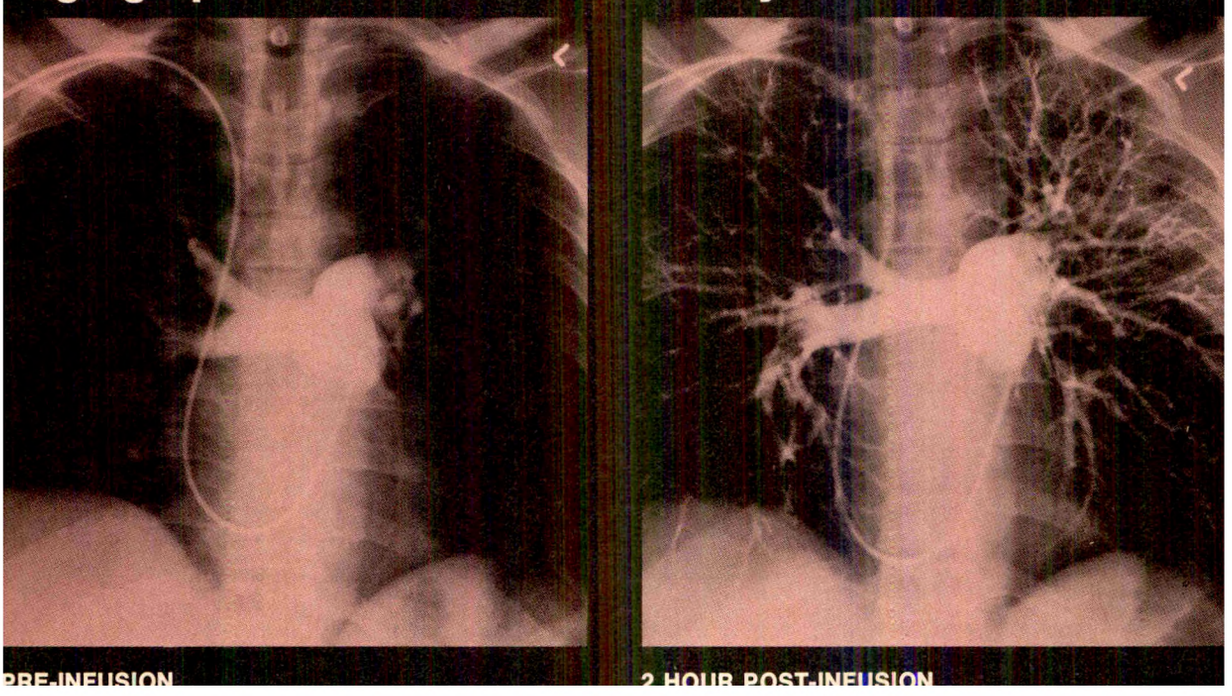
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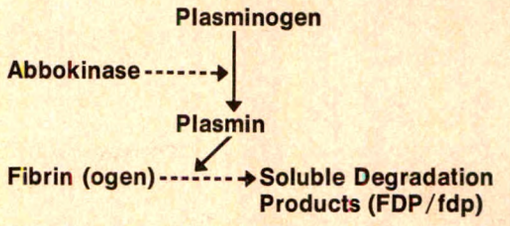
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Diagrammatic representation of the activation of plasminogen by Abbokinase, and the degradation of fibrin (ogen) by plasmin.

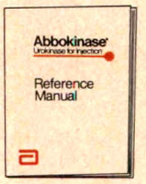
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Abbokinase is not a foreign protein. Originally derived from human urine, it is now obtainable from human kidney cells by tissue culture techniques developed by Abbott Laboratories.

Unlike streptokinase, Abbokinase has been associated with few allergic responses. Induced antibody formation is not seen in intradermal tests.

To make Abbokinase readily available throughout the U.S., it initially will be distributed from North Chicago, Illinois and 45 strategically located hospitals. For a copy of the ABBOKINASE REFERENCE MANUAL, please write Medical Services Department, Abbott Laboratories, Pharmaceutical Products Division, North Chicago, Ill. 60064.



8013241

References

1. McNicol, G. P., The Fibrinolytic Enzyme System, *Postgraduate Medicine*, August, 1973 (supplement). **2.** Aoki, N., et al, The Behavior of a 2-Plasmin Inhibitor in Fibrinolytic States, *Journal of Clinical Investigation*, 60:361-369, 1977. **3.** Chesterman, C. N., et al, Relationship of Plasminogen Activator to Fibrin, *Nature* (New Biol.), 238:15-17, 1972.

Please see following page for Brief Summary

ABBOTT

Abbokinase®
Urokinase for Injection

Brief Summary

ABBOTT

8013241

ABBOKINASE (urokinase for injection) should only be used by physicians with wide experience in the management of thrombotic disease in hospitals where the recommended clinical and laboratory monitoring (see WARNINGS, PRECAUTIONS and DOSAGE AND ADMINISTRATION) can be performed.

When considering treatment with urokinase, the physician should carefully assess the overall clinical status and history of the patient. The hemostatic capability of the patient is more profoundly altered and bleeding more frequent with urokinase therapy than with heparin or oral coumarin anticoagulant therapy. When bleeding occurs it is also more severe and more difficult to manage. The potential risk of serious hemorrhage relative to such factors as age, physical condition, and underlying bleeding tendency of the patient (as described under WARNINGS and PRECAUTIONS) should be weighed against the potential benefits of treating the patient with urokinase.

INDICATIONS

Pulmonary Embolism

ABBOKINASE (urokinase for injection) is indicated in adults:

- for the lysis of acute massive pulmonary emboli, defined as obstruction or significant filling defects involving two or more lobar pulmonary arteries or an equivalent amount of emboli in other vessels.[8]
- for the lysis of pulmonary emboli accompanied by unstable hemodynamics, i.e., failure to maintain blood pressure without supportive measures.

The diagnosis should be confirmed by objective means, preferably pulmonary arteriography.

Urokinase treatment should be instituted as soon as possible after onset of pulmonary embolism, and no later than five days after onset. Under these circumstances, angiographic and hemodynamic measurements demonstrate a more rapid improvement during the first 24 hours of therapy than with heparin therapy (Table I).[7-9] However, it has not been established that treatment with urokinase decreases morbidity or mortality, when compared to heparin therapy alone.

TABLE I †

	UPET*	USPET**	
	Heparin	12-Hour Urokinase	12-Hour Urokinase	24-Hour Urokinase
Change in angiographic severity score based on 4-point system	0.54	1.78	1.66	1.76
Decrease in relative percentage perfusion defect on lung scans	8.3	24.1	20	29.2
Change in pulmonary artery pressure (mm Hg)	—1.1	—6.2	—7.28	—7.53
Change in cardiac index (l/min/m²)	—0.05	+0.02	+0.06	+0.30

*Urokinase pulmonary embolism trial.
**Urokinase-streptokinase pulmonary embolism trial.

Evaluations were obtained between 18 and 30 hours after the start of therapy. After several days, there were no differences between the results in the heparin treated patients and those receiving urokinase.

† Adapted from (7).

CONTRAINDICATIONS — Because thrombolytic therapy increases the risk of bleeding, urokinase is contraindicated in the following situations:

1. Surgery within ten days. Liver or kidney biopsy, lumbar puncture, thoracentesis or paracentesis, extensive or multiple cutdowns should be considered surgical procedures.
2. Intraarterial diagnostic procedure within ten days.
3. Ulcerative wound.
4. Recent trauma with possibility of internal injuries.
5. Visceral or intracranial malignancy.
6. Pregnancy and the first ten days of the post-partum period.
7. Ulcerative colitis, diverticulitis or an actively bleeding lesion (or one with a significant potential for bleeding) of the gastrointestinal or genitourinary tract.
8. Severe hypertension.
9. Acute or chronic hepatic or renal insufficiency.
10. Uncontrolled hypocoagulable state, including one that may be caused by a coagulation factor deficiency, thrombocytopenia, spontaneous fibrinolysis, or another purpuric or hemorrhagic disorder.
11. Chronic lung disease with cavitation, e.g., tuberculosis.
12. Subacute bacterial endocarditis or rheumatic valvular disease.
13. Recent cerebral embolism, thrombosis or hemorrhage. Treatment with urokinase is contraindicated for at least two months after cerebral embolism, thrombosis or hemorrhage because patients with cerebral infarction remain at risk of bleeding into the infarcted tissue.
14. Any other condition in which bleeding might constitute a significant hazard or be particularly difficult to manage because of its location.

The conditions listed above should not be regarded as absolute contraindications. Rather, the risk of hemorrhage must be weighed carefully against the anticipated benefits of urokinase therapy in an individual patient and the benefits and risks associated with the use of urokinase should be compared to the benefits and risks associated with other forms of therapy.

WARNINGS

Bleeding

Activation of the fibrinolytic system with urokinase results in a more profound alteration of the hemostatic status of the patient than does anticoagulant therapy with heparin or coumarin agents. The aim of urokinase therapy is the production of sufficient amounts of plasmin for the lysis of intravascular deposits of fibrin; however, fibrin deposits which provide hemostasis, for example, at sites of needle punctures, are also destined for lysis, and bleeding from such sites may occur. The possibility of bruising or hematoma formation, especially with intramuscular injections, is high during thrombolytic therapy. Unnecessary handling of the patient should be avoided. Strict attention should be given to this section and the CONTRAINDICATIONS section in order to minimize the risk of bleeding.

Because of the high risk of hematoma formation, intramuscular injections must be avoided during urokinase therapy, as with heparin therapy. Bleeding at sites of recent invasive procedures may occur. Hence, arterial invasive procedures must also be avoided before and during treatment with urokinase. Should an arterial puncture be *absolutely* necessary, the femoral artery must be avoided and the radial or brachial artery used. It should be done carefully by a physician experienced in such a procedure. Pressure should be applied for at least 15 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding. Also, venipunctures should be performed as carefully and infrequently as possible. If the bleeding from an invasive site is not serious, treatment may be continued with appropriate clinical observation. Local measures, i.e., pressure, should be initiated immediately.

Spontaneous bleeding from internal sites (not accessible for pressure application) may also occur. The risk of spontaneous bleeding is greater in patients with pre-existing hemostatic defects, e.g., patients with histories suggestive of prior bleeding problems, with or without demonstrable abnormalities in platelet count, prothrombin time, partial thromboplastin time, or bleeding time. Such patients should be assessed carefully before initiating treatment with urokinase.

In addition to its fibrinolytic action, plasmin also degrades fibrinogen, Factor V, Factor VIII, and other proteins. The products of plasmin degradation of fibrinogen and fibrin (FDP/fdp) possess an anticoagulant effect. Bleeding may be difficult to control because of this anticoagulant effect.

Should serious spontaneous bleeding occur, the infusion of urokinase should be terminated immediately, and treatment instituted as described under ADVERSE REACTIONS.

Predispositon to Cerebral Embolism

Treatment with urokinase of patients with atrial fibrillation or other conditions in which there is possible risk of cerebral embolism may be hazardous because of the risk of bleeding into the infarcted area.

Use of Anticoagulants

Concurrent use of anticoagulants with urokinase is not recommended and may be hazardous. Before starting urokinase in patients being treated with heparin, the effects of heparin should be allowed to diminish with time. As a general rule, a thrombin time of *less than twice* the normal control value is adequate for starting urokinase infusions safely. Similarly, heparin should not be started following urokinase therapy until the thrombin time has returned to *less than twice* the normal control value.

Rethrombosis has been observed after termination of urokinase treatment. In order to minimize this risk, the use of intravenous heparin followed by oral anticoagulant therapy is considered a necessary adjunct following urokinase therapy (see DOSAGE AND ADMINISTRATION).

Use in Pregnancy

See CONTRAINDICATIONS.

Use in Children

Safety and effectiveness of urokinase therapy in children have not been established; therefore, treatment of such patients is not recommended.

PRECAUTIONS

Drug Interactions

Concurrent use of drugs that may alter platelet function, e.g., aspirin, indomethacin, and phenylbutazone, should be avoided. The interaction of ABBOKINASE (urokinase for injection) with other drugs has not been studied.

Laboratory Monitoring

In patients who have received heparin, the thrombin time should be measured prior to starting urokinase. (See WARNINGS.) Similarly, the thrombin time should be monitored following urokinase therapy prior to instituting heparin. (See DOSAGE AND ADMINISTRATION.) During urokinase administration, the levels of fibrinogen, plasminogen, Factor V, and Factor VIII are usually substantially diminished. Concomitantly, the level of fibrin(ogen) degradation products (FDP/fdp) is increased. The combination of reduced fibrinogen and increased FDP/fdp results in a prolongation of the thrombin time. While changes in any of these parameters may serve as confirmation of the existence of a lytic state, no adjustment of dosage should be made on the basis of these test results.

ADVERSE REACTIONS

Incidence and Management

Strict observance of the contraindications, warnings, and precautions to the use of urokinase is essential to minimize the incidence and severity of adverse effects.[7]

BLEEDING

Incidence

Where thrombolytic agents (streptokinase and urokinase) were used in the same controlled clinical trial, severe bleeding (patients receiving a transfusion of greater than two units of blood) was seen in 4 and 6%, respectively. Several fatalities due to cerebral hemorrhage have occurred during urokinase therapy.

Less severe spontaneous bleeding has been observed during urokinase treatment at approximately twice the frequency as that occurring during heparin therapy. Oozing of blood from sites of percutaneous trauma is frequent; hence, all invasive procedures, especially arterial punctures and intramuscular injections must be avoided and intravenous punctures kept to a minimum before and during treatment with urokinase.

A moderate decrease in hematocrit not accompanied by clinically detectable bleeding occurred in approximately one out of five patients treated with urokinase.

Management of Severe Bleeding

In case of serious bleeding, urokinase therapy must be discontinued. If blood loss has been large, packed red cells are indicated. Plasma volume expanders (other than Dextran) are indicated to replace blood volume deficit. If only whole blood is available, it may also be used. Although the use of aminocaproic acid (ACA, AMICAR®) in humans as an antidote for urokinase has not been documented, it may be considered if the hemorrhage is unresponsive to blood replacement. (See WARNINGS.)

ALLERGIC REACTIONS

Although urokinase is a protein of human origin, and *in vitro* tests with the drug, as well as intradermal test in humans, gave no evidence of induced antibody formation, the possibility of serious allergic reactions (including anaphylaxis) occurring with its use cannot be excluded. Relatively mild allergic reactions, e.g., bronchospasm and skin rash, were reported rarely.

FEVER

Febrile episodes occurred in approximately two to three out of 100 patients. A cause and effect relationship has not been established. Symptomatic treatment is usually sufficient to alleviate discomfort. The use of acetaminophen rather than aspirin is recommended.

DOSAGE AND ADMINISTRATION

Dosing

ABBOKINASE IS INTENDED FOR INTRAVENOUS INFUSION ONLY.

A priming dose of 2,000 I.U./lb (4,400 I.U./kg) of ABBOKINASE is given as the Abbokinase-Normal Saline admixture over a period of ten minutes. This is followed by a continuous infusion of 2,000 I.U./lb/hr (4,400 I.U./kg/hr) of ABBOKINASE (given as the Abbokinase-Normal Saline admixture) for 12 hours. The total volume of fluid administered should not exceed 200 ml.

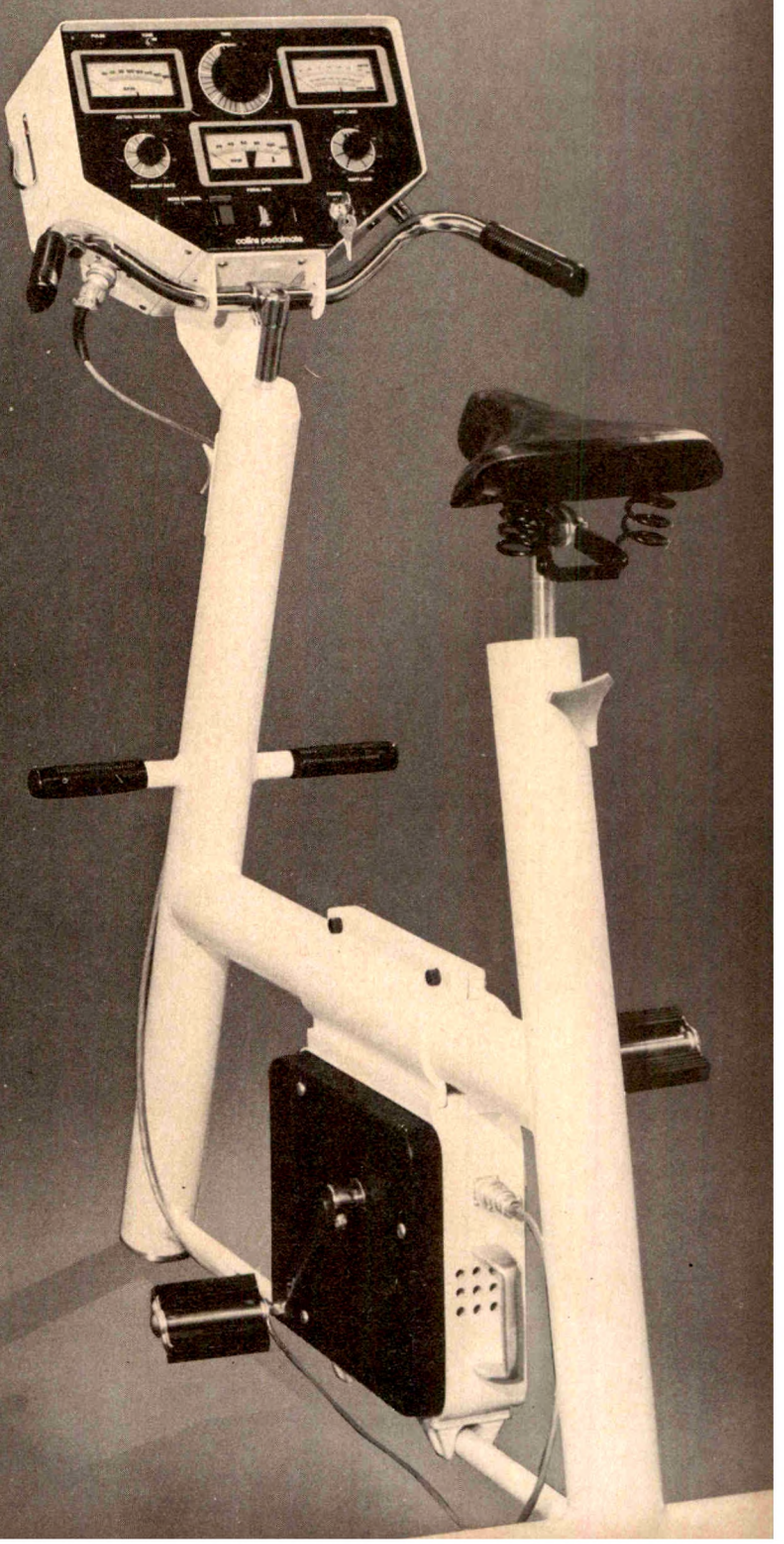
Administer ABBOKINASE (urokinase for injection) by means of a constant infusion pump that is capable of delivering a total volume of 195 ml.

Anticoagulation After Terminating Urokinase Treatment

At the end of urokinase therapy, treatment with heparin by continuous intravenous infusion is recommended. Heparin treatment should not begin until the thrombin time has decreased to *less than twice* the normal control value. See manufacturer's prescribing information for proper use of heparin.

PERFORMING *STRESS* TESTS?

CONTROL THEM WITH *COLLINS*



Stress testing requires accurate control and monitoring of cardiac output. That means utilizing an exercise device which will maintain the subject's heart rate at a constant BPM by varying the work load. That means Pedalmate!

The Pedalmate is an ergometer which offers two modes of operation. In the 'Heart Rate Control Mode,' the work load is automatically varied by means of a feedback control signal which is proportional to the difference between the subject's actual heart rate and a preset, selectable heart rate. The subject's actual heart rate is detected by a blood pressure wave transducer which attaches comfortably to the earlobe. The fine adjustment in work load makes it possible to exercise the subject at a preset heart rate level for a preselected time.

When in the 'Manual Mode,' the Pedalmate presents the subject a constant load (manually variable) which remains constant independent of pedal rate.

SPECIFICATIONS

Heart Rate Control Accuracy:	±5 BPM
Heart Rate Accuracy:	±2% of reading
Watt Load Accuracy:	±5% of reading
Pedal Rate Accuracy:	±2% of reading (0-120 rpm)
Heart Rate Range:	40 to 180 BPM
Watt Load Range:	25 to 200 watts (150 to 1200 KPM/min.)
Pedal rpm Range:	0-120 rpm (30-120 rpm constant work)
Timer Range:	0 to 30 minutes
Lamp Indicators:	AC Power Lamp, Heart Beat LED, Heart Control Program Run Lamp
Meters:	Heart Rate (BPM), Pedal Rate (rpm), Work Load (watts)
Other Controls:	Mode Select Switch, Preset Heart Rate Dial, Manual Watt Load Control, Key Power Switch
Output Signals:	Heart Rate CAL Factor = 1 BPM/50 mv. Watt Load CAL Factor = 1 watt/50 mv.

For additional information, write or call

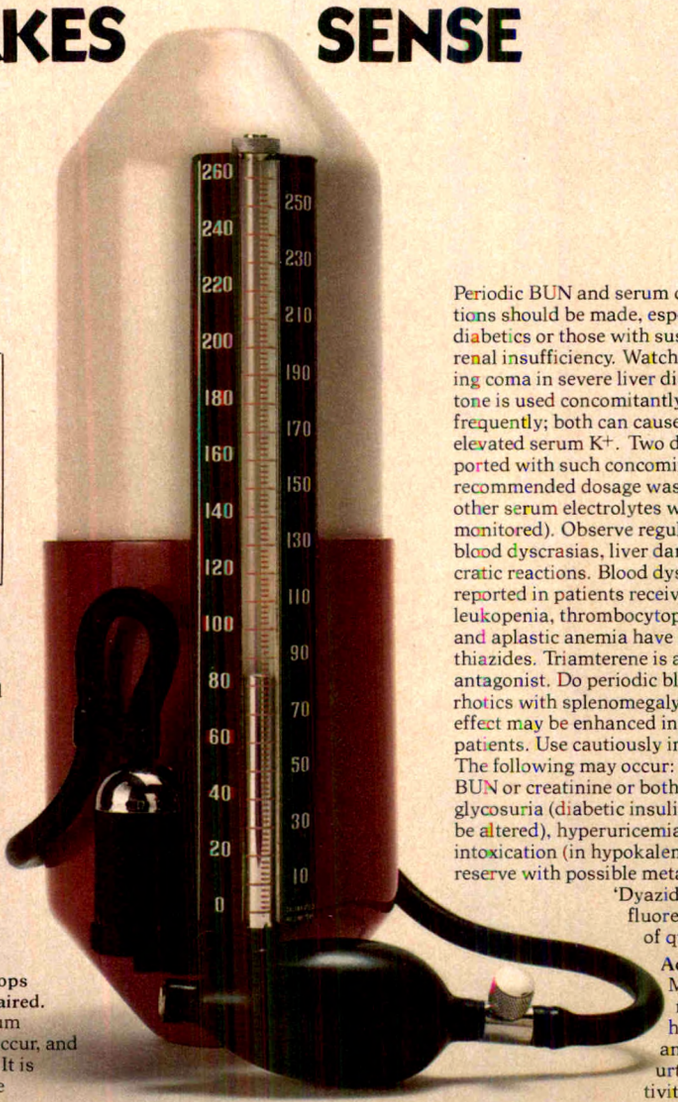
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Each capsule contains 50 mg. of Dyrenium® (triamterene, SK&F Co.) and 25 mg. of hydrochlorothiazide.

MAKES SENSE



Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. A brief summary follows:

* **Warning**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

* **Indications:** When the combination represents the dosage determined by titration: Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, the nephrotic syndrome. Corticosteroid and estrogen-induced edema, idiopathic edema; hypertension, when the potassium sparing action of triamterene is warranted. (See Box Warning.) Routine use of diuretics in healthy pregnant women is inappropriate; they are indicated in pregnancy only when edema is due to pathological causes.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

FOR LONG-TERM CONTROL OF HYPERTENSION.* SERUM K^+ AND BUN SHOULD BE CHECKED PERIODICALLY. (SEE WARNINGS SECTION.)

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PACEMAKERS

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Siemens-Elema introduced the first implantable pacemaker designed by Dr. Elmquist and implanted by Dr. Senning at the University Hospital Karolinska, Stockholm.

Since then, Siemens-Elema's engineers have continuously, in cooperation with foremost cardiologists and surgeons, developed reliable products to be known worldwide.

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Siemens-Elema introduced a long-term transvenous lead, which became known as an extremely reliable Elema endocardial lead.

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Siemens-Elema introduced an implantable atrial triggered pacemaker.

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Siemens-Elema introduced a pacemaker with a Lithium battery, developed for long-term stimulation.

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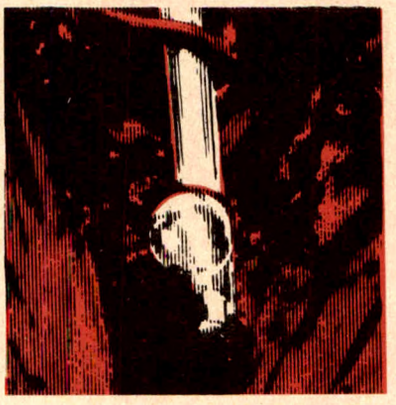
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- Theoretical life expectancy of more than 11 years. (Calculated under worst case 100% stimulation.)
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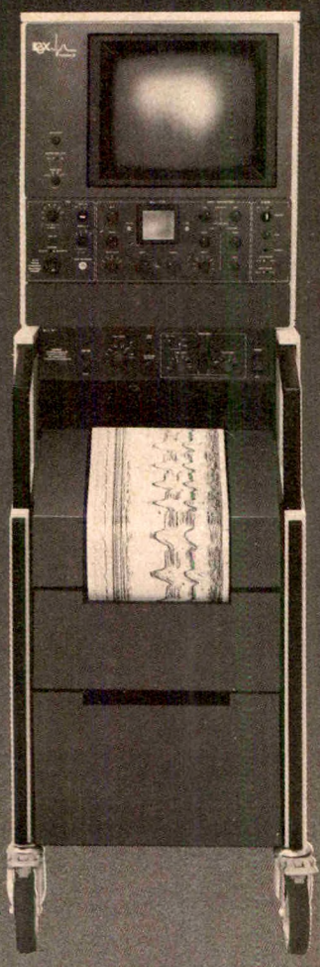
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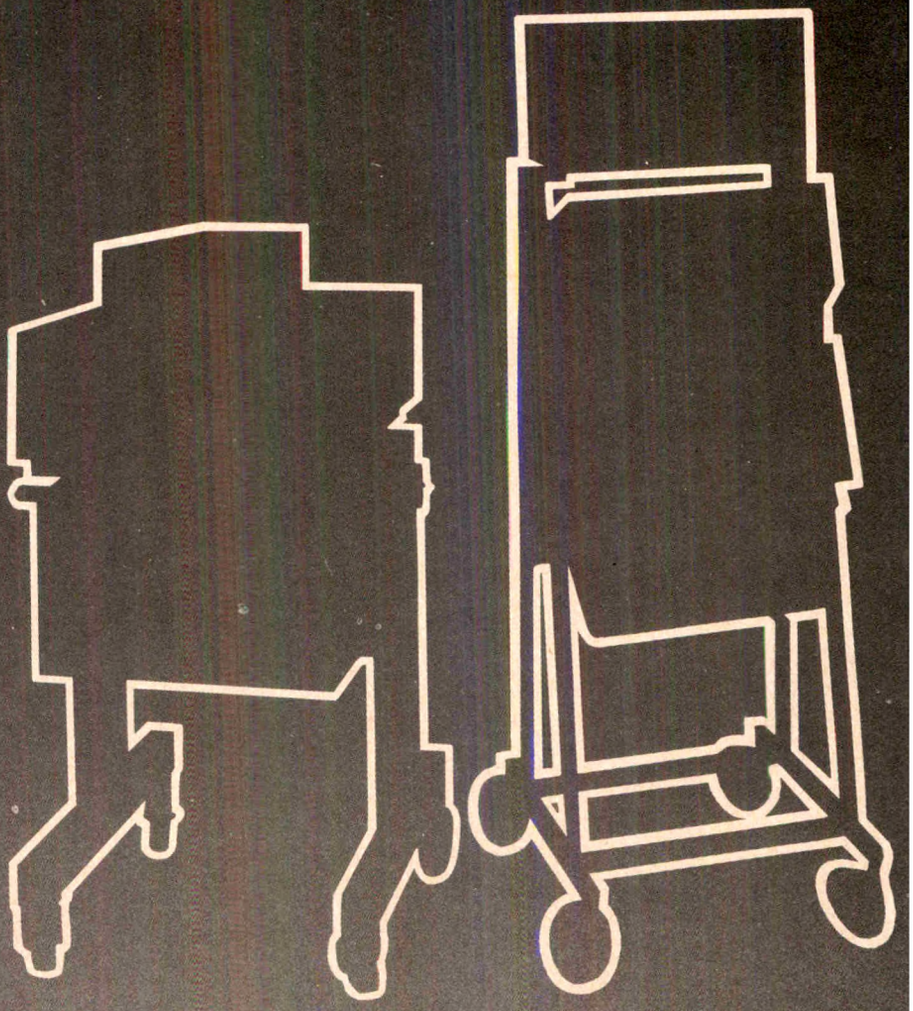
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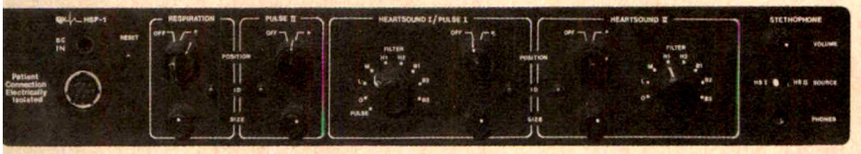
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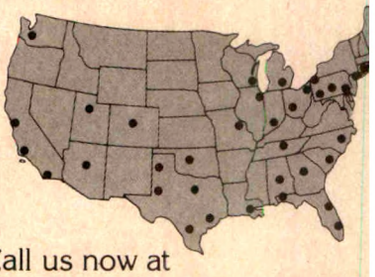
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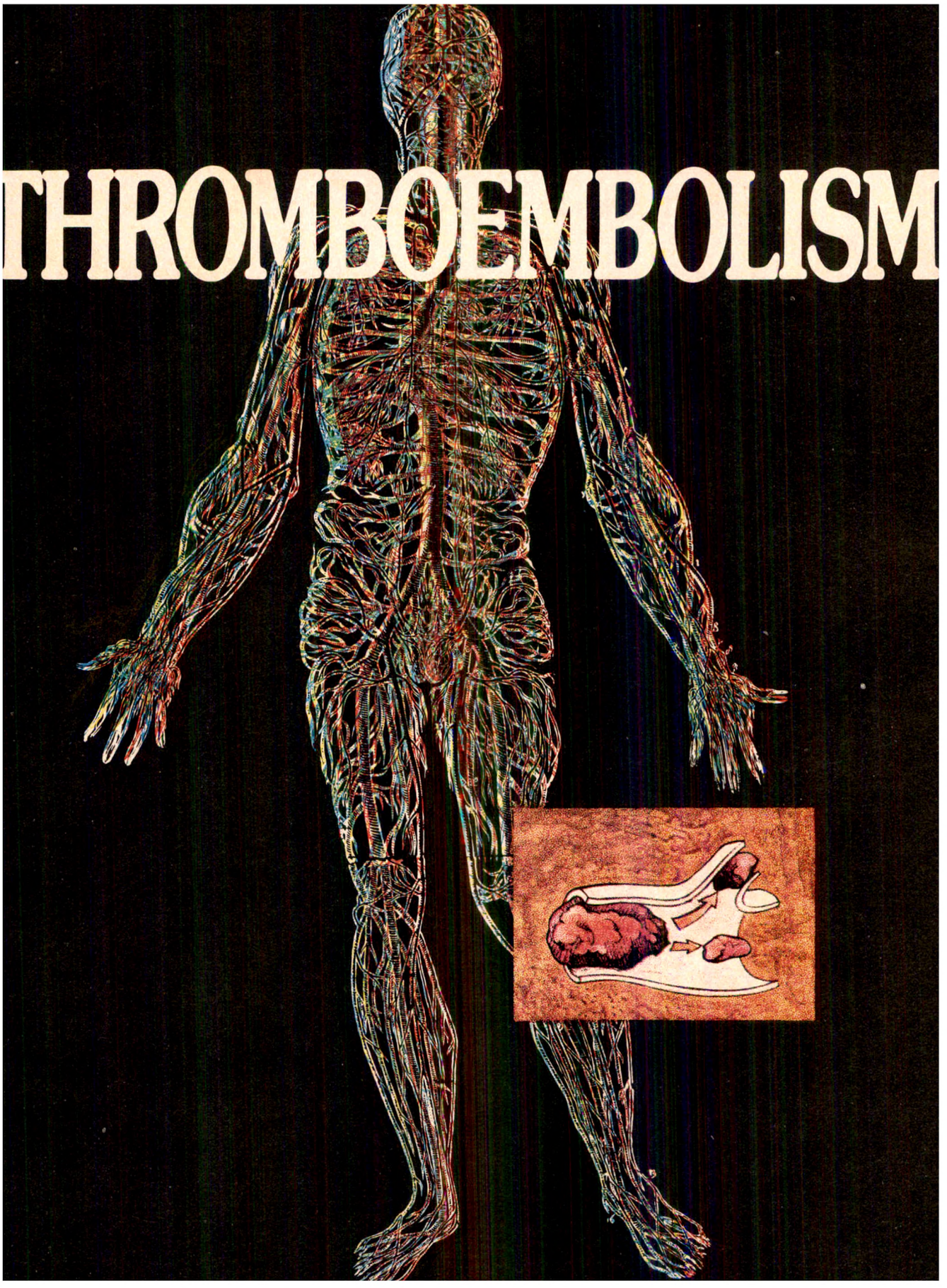
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THROMBOEMBOLISM



COUMADIN® (CRYSTALLINE SODIUM WARFARIN U.S.P.)

FOR ORAL ANTICOAGULATION

Prophylactic Use

A number of cardiac syndromes can predispose patients to thromboembolic episodes. The greatest threat of thromboembolism, however, exists in patients with a history of obesity, excessive cigarette smoking or previous episodes of venous thrombosis or pulmonary embolism. Postoperative patients requiring extended immobilization and the elderly are at high thromboembolic risk as are the severely injured—particularly those over 40 years with fractures of the hip, pelvis or lower extremities—and patients undergoing elective cup arthroplasty or pelvic surgery.

Emphasis should be placed on prophylaxis for those patients predisposed to thromboembolism. The oral anticoagulant of choice is COUMADIN® (crystalline sodium warfarin U.S.P.)

Therapeutic Use

For established thromboembolism, administration of I.V. heparin followed by oral anticoagulant therapy is a cornerstone of treatment. COUMADIN,® a chemically pure oral anticoagulant with high predictability of response, is a mainstay of effective therapy.

Dosage and Administration

In patients receiving COUMADIN,® prothrombin time should be maintained at 1.5 to 2.5 times the control until results stabilize. Dosage and administration should be individualized according to prothrombin time results and reevaluated periodically throughout therapy.

Patients should be well informed about their condition and medication, since factors such as dietary change, travel, other medication, change in physical condition and abrupt environmental change may influence prothrombin time and, therefore, response to COUMADIN.®

The oral anticoagulant of choice COUMADIN®

(CRYSTALLINE SODIUM WARFARIN U.S.P.)

Endo Laboratories, Inc.

Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

DUPONT

Before prescribing, please see prescribing information on following page.

COUMADIN® is an Endo registered U.S. trademark;
U.S. Pat. No. 3,077,481 (Reissue No. 25,866)

COUMADIN®

(CRYSTALLINE SODIUM WARFARIN*)

DESCRIPTION COUMADIN® (crystalline sodium warfarin), a prothrombinopenic anticoagulant, is chemically crystalline sodium warfarin isopropanol clathrate. The crystallization of sodium warfarin virtually eliminates trace impurities present in amorphous sodium warfarin, thus achieving a crystalline product of the highest purity. Warfarin* is the coined generic name for 3-(α-Acetonylbenzyl)-4-hydroxycoumarin. On a dose-for-dose basis, COUMADIN® (crystalline sodium warfarin) is therapeutically equivalent to amorphous sodium warfarin.

ACTIONS COUMADIN® and other coumarin anticoagulants act by depressing synthesis in the liver of several factors which are known to be active in the coagulation mechanisms in a variety of diseases characterized by thromboembolic phenomena. The resultant **in vivo** effect is a sequential depression of Factors VII, IX, X and II. The degree of depression is dependent upon the dosage administered. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombosis has occurred, anticoagulant treatment aims to prevent further extension of the formed clot and prevents secondary thromboembolic complications which may result in serious and possible fatal sequelae.

After oral administration, absorption is essentially complete, and maximal plasma concentrations are reached in 1 to 9 hours. Approximately 97% is bound to albumin within the plasma. COUMADIN® usually induces hypoprothrombinemia in 36 to 72 hours, and its duration of action may persist for 4 to 5 days, thus producing a smooth, long lasting response curve. Little is known of the metabolic pathways involved in the biotransformation of oral anticoagulants in man. However, their metabolites appear to be eliminated principally in the urine.

INDICATIONS Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN® is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Pregnancy—COUMADIN® (crystalline sodium warfarin) is contraindicated in pregnancy because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy. Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms–cerebral, dissecting aorta; (4) pericarditis and pericardial effusions; (5) subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis; or lack of patient cooperation. **Spinal puncture** and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding. **Miscellaneous:** polyarthritis, vitamin C deficiency, major regional, lumbar block anesthesia and malignant hypertension.

WARNINGS Sodium warfarin is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN® are given together, a period of 4 to 5 hours should elapse after the last intravenous dose and 12 to 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when sodium warfarin is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:
Lactation–coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Prolonged dietary deficiency** (cachexia, vitamin K). **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**–sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, menometrorrhagia, allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN®, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN*.

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders–infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency–steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cinchophen; clofibrate; COUMADIN* overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methyldopa; methylphenidate; metronidazole; monoamine oxidase inhibitors; nalidixic acid; oxolinic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates; sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; trimethoprim/sulfamethoxazole; unreliable prothrombin time determinations.

†Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN® underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN®. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN® (crystalline sodium warfarin) include:

1. Minor or major hemorrhage from any tissue or organ–which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and an extremely rare reaction consisting of hemorrhagic infarction and necrosis of the skin.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN* patient aids are available to physicians on request.

The administration and dosage of COUMADIN® must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K dependent Factors VII, X and II. These factors, in addition to Factor IX, are affected by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN® should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic prothrombinopenia are 1½ to 2½ times the normal prothrombin time (e.g. 21 to 35 seconds, with a control of 14 seconds).

Induction–40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Maintenance–Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy–The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery–The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN® be adjusted to maintain the prothrombin time at approximately 1½ to 2 times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN* with Heparin–Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in situations of great emergency to administer sodium heparin initially along with COUMADIN®. The initial dose of heparin and injectable COUMADIN* may be administered together in the same syringe. It should be noted that heparin may affect the prothrombin time, and therefore, when patients are receiving both heparin and COUMADIN*, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, and preferably 4 to 5 hours after the last intravenous injection or 12 to 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN® (crystalline sodium warfarin), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN* may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN® administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can be obtained.

SUPPLIED Tablets: COUMADIN® (crystalline sodium warfarin). For oral use, single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white, 25 mg red. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100.

Injection: Available as single injection units of amorphous sodium warfarin lyophilized for intravenous or intramuscular use in a box of 6 units for use immediately after reconstitution. 50 mg: Unit consists of 1 vial, 50 mg; sodium chloride, 10 mg; thimerosal, 0.2 mg. pH is adjusted with sodium hydroxide; accompanied by a 2 ml ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

*Present as crystalline sodium warfarin isopropanol clathrate.

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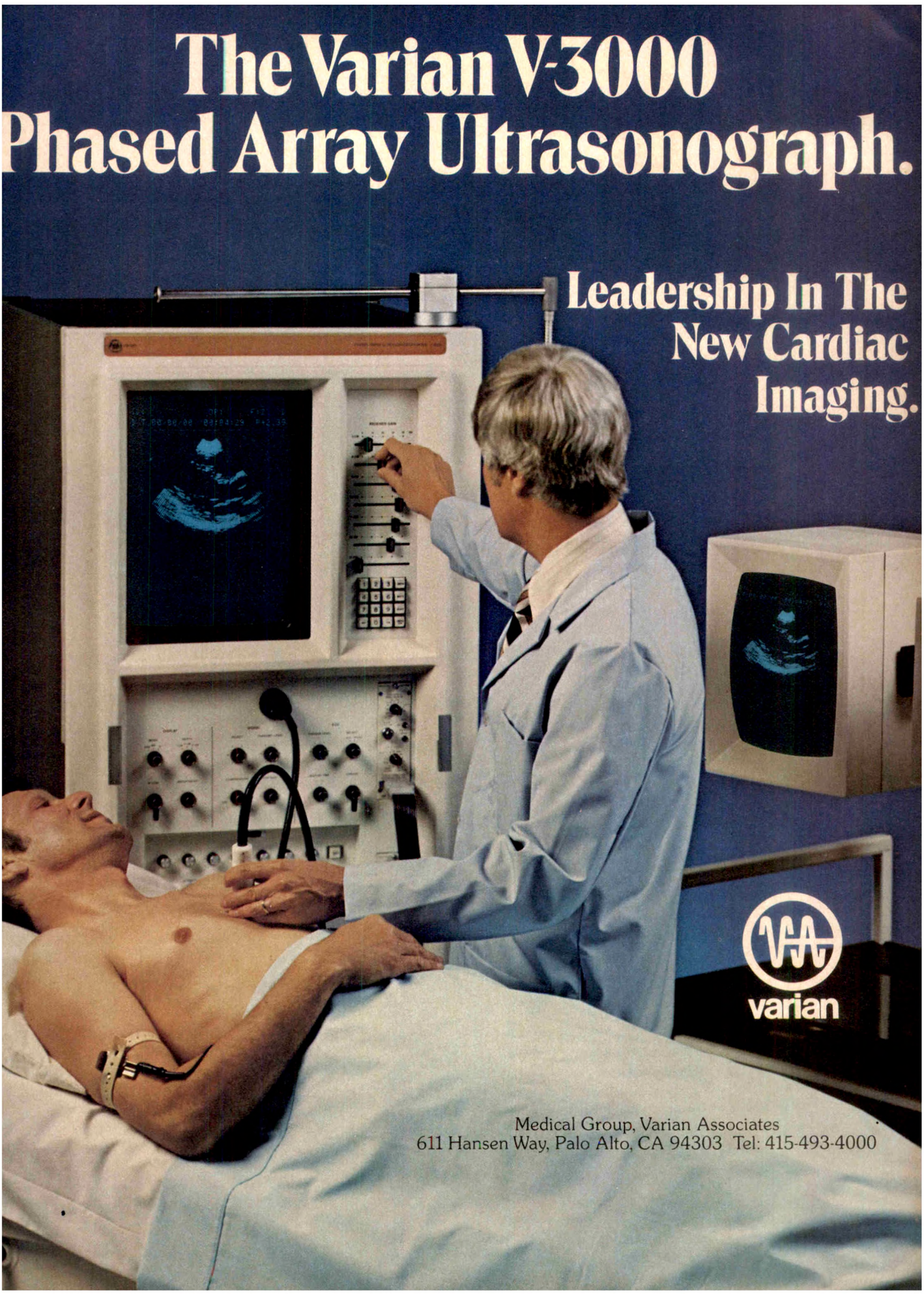
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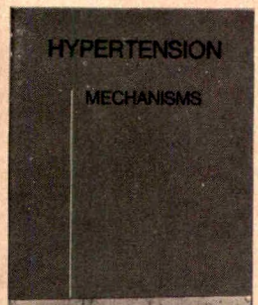
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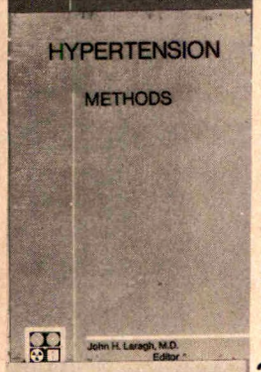
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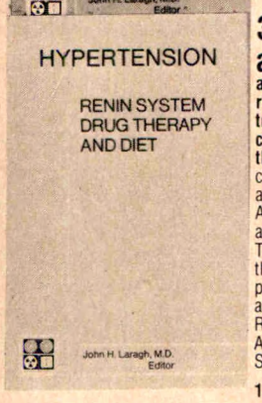
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ALDACTONE®
(spironolactone) 25 mg. tablets

WARNING
Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats (see *Warnings*). Aldactone should be used only in those conditions described under *Indications*. Unnecessary use of this drug should be avoided.

Indications: Diagnosis and treatment of primary hyperaldosteronism. Essential hypertension, edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate. Cirrhosis of the liver accompanied by edema and/or ascites. Hypokalemia.

Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, or hyperkalemia.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactone. Do not administer concurrently with other potassium-sparing diuretics.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75, and 250 times the usual daily human dose (2 mg./ kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hyponatremia may be caused or aggravated, especially when Aldactone is administered in combination with other diuretics. Transient elevation of BUN and/or mild acidosis may occur. Aldactone potentiates the effect of other diuretics or antihypertensive agents, particularly ganglionic blocking agents; therefore the dosage of such drugs should be reduced by at least 50 percent when adding Aldactone. Gynecomastia may develop and in rare instances some breast enlargement may persist. Vascular responsiveness to norepinephrine may be reduced.

Spironolactone may cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazard to the fetus. Breast feeding should be discontinued when Aldactone is being used.

Adverse Reactions: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established. Adverse reactions are usually reversible upon discontinuation of the drug.

Dosage and Administration

For primary hyperaldosteronism: 400 mg. daily for three to four weeks (long test), or for four days (short test). For preparation for surgery or for long-term maintenance therapy, 100 to 400 mg. daily.

For edema in adults: Initial daily dosage is 100 mg. in divided doses but may range from 25 to 200 mg. daily. If after five days an adequate diuretic response has not occurred, a second diuretic which acts more proximally in the renal tubule may be added. The dosage of Aldactone should remain unchanged when other diuretic therapy is added.

For edema in children: Initial daily dosage should provide approximately 1.5 mg. per pound of body weight (3.3 mg./kg.) in divided doses.

For essential hypertension: Initial adult daily dosage of 50 to 100 mg. in divided doses, alone or with diuretics which act more proximally in the renal tubule, or with other antihypertensive agents. Continue treatment for at least two weeks since maximal response may not occur before this time. Adjust subsequent dosage according to patient response.

For hypokalemia: 25 to 100 mg. daily in divided doses.

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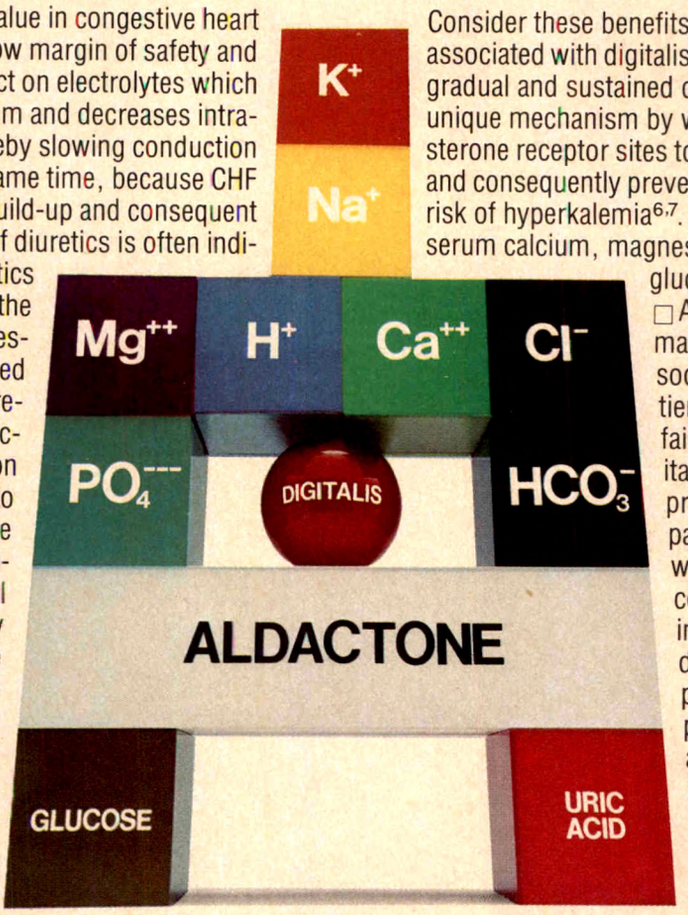
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The Delicate Balance.

Unfortunately, electrolyte imbalance is often a problem during digitalis therapy. And most diuretics worsen the problem.

Despite its therapeutic value in congestive heart failure, digitalis has a narrow margin of safety and toxic levels produce an effect on electrolytes which increases intracellular sodium and decreases intracellular potassium, thereby slowing conduction in cardiac tissues. At the same time, because CHF encourages sodium build-up and consequent edema, concomitant use of diuretics is often indicated. □ Use of most diuretics can increase problems for the patient on digitalis, and excessive loss of potassium caused by potent diuretics is a frequent cause of digitalis toxicity.[1,2] Potassium depletion sensitizes the myocardium to digitalis and can set the stage for serious cardiac arrhythmias even with normal dosage.[3] □ Clearly, any diuretic choice should be carefully analyzed for its effect on electrolyte balance. Thiazides, for example, can induce hypokalemia, hypercalcemia, hypomagnesemia, and hypophosphatemia.[4] They can also decrease uric acid excretion and impair glucose tolerance. In treatment with furosemide, too, fluid and electrolyte imbalance is the most common form of clinical toxicity.[5]



Fortunately, concomitant diuretic therapy with Aldactone® (spironolactone) can help maintain the delicate electrolyte balance... when other measures won't do.

Consider these benefits in avoiding the problems associated with digitalis therapy: Aldactone provides gradual and sustained diuresis...works through a unique mechanism by which it competes for aldosterone receptor sites to normalize body potassium, and consequently prevents hypokalemia with limited risk of hyperkalemia[6,7]...does not adversely affect serum calcium, magnesium and uric acid levels or glucose tolerance.[7] □ Aldactone is indicated for management of edema and sodium retention in those patients with congestive heart failure who are taking digitalis, or in the treatment or prevention of hypokalemia in patients taking digitalis, when other measures are considered inadequate or inappropriate. □ When diuretic therapy is indicated, prescribe Aldactone to help preserve the delicate balance of electrolytes during digitalis therapy.

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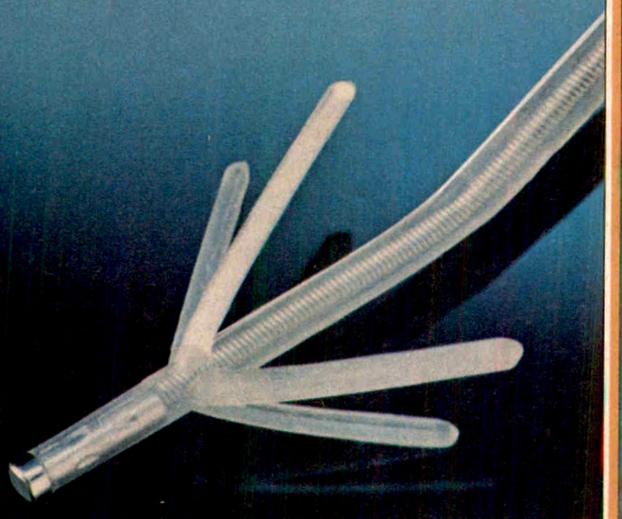
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(spironolactone) 25 mg. tablets

Before prescribing, please consult the complete prescribing information, a brief summary of which follows.

An Endocardial Tined Ventricular Lead.

The Medtronic® 6950 and 6951 unipolar and bipolar tined leads feature four integral silicone rubber tines that protrude from the lead body just proximal to the tip electrode. These tines were designed to provide better acute lead stability and reduce chronic lead dislodgement by latching onto the papillary musculature or the trabeculae of the right ventricle. The large surface area provided by the tines should also enhance the stability afforded by fibrosis.



A Small, Durable Endocardial Tined Lead.

The newest members of the Tenax™ family of self-anchoring leads – the 6961 and 6962 unipolar and bipolar leads – feature shorter, smaller tines and small tip diameter (8 French; approximately 10 French with tines folded) enabling the physician to use the more common cephalic approach. Though small, the soft, pliable tines are still long enough to become securely anchored in one or more of the interstitial spaces formed by the trabeculae of the right ventricular chamber. The lead's ring-tipped electrode provides optimum energy to the heart with improved sensing and current drain characteristics. Its durable, space-wound multifilar conductor is designed to provide a longer flex life to match the potential long effective service life of lithium powered pulse generators.



TOUGH & TENACIOUS

The TENAX™ Family of Self-Anchoring Leads from Medtronic.

Our entire family of Medtronic Tenax™ leads has one common trait:
Tenacious, positive-anchoring lead tips.
Tips designed to minimize dislodgement problems associated with standard endocardial pacing leads.
Tips that stay where you put them.

MEDTRONIC IMPLANTABLE PACING LEADS

Intended Use

Medtronic implantable pacing leads are designed to be used with Medtronic pulse generators as part of a cardiac pacing system (see product labeling for specific directions regarding applications).

Contraindications

Endocardial pacing leads are contraindicated in the presence of tricuspid valvular disease.

Myocardial leads are contraindicated for a patient whose myocardium is thin-walled, suffused with fat, or infarcted in the area of electrode placement.

Myocardial leads may be contraindicated in the older high risk patients with a low tolerance to general anesthesia.

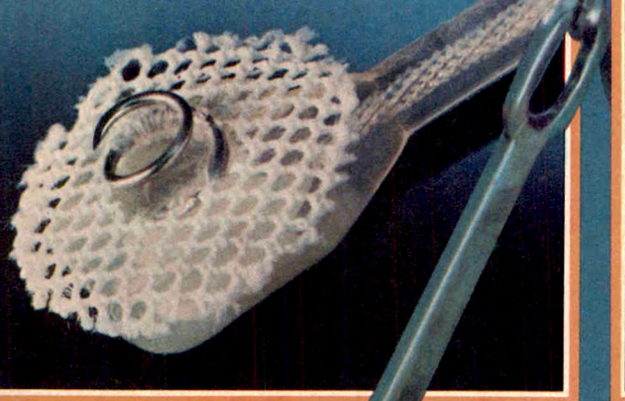
Atrial J-leads are contraindicated in the absence of a right atrial appendage.

Warnings

An implanted lead constitutes a direct, low resistance current path to the myocardium

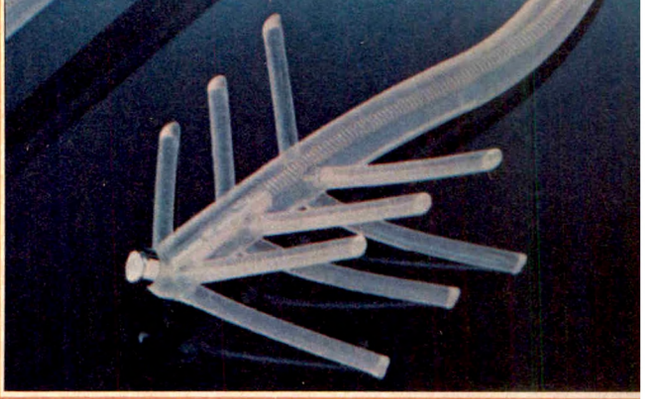
A Unique Sutureless Myocardial Lead.

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A Tined Endocardial Atrial J-Shaped Lead.

The Medtronic 6991 unipolar and 6990 bipolar leads are molded into a J configuration to facilitate placement and lodging into the right atrial appendage. During insertion, the J tip is straightened by means of lead stylets. The distal end of the J contains a series of nine silicone rubber tines; the electrode tip is canted inward so the force exerted by the tines will enable the electrode to contact the endocardial surface of the atrium. After the lead tip has been advanced into the desired position, the stylets are partially withdrawn to allow the lead to assume its natural J shape. The tines are fixed into the atrial appendage by becoming anchored in one or more of the interstitial spaces formed by trabeculae.



For further information on the Medtronic Tenax™ lead family, contact your Medtronic, Inc. representative or write for a complete technical brochure.

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uring the connection and testing procedures, only battery-powered pulse generators hould be used with the lead system to protect against ventricular fibrillation induced by lternating current leakage. Extreme caution must be taken to properly ground all ne-powered equipment used in the vicinity of the patient.

recautions

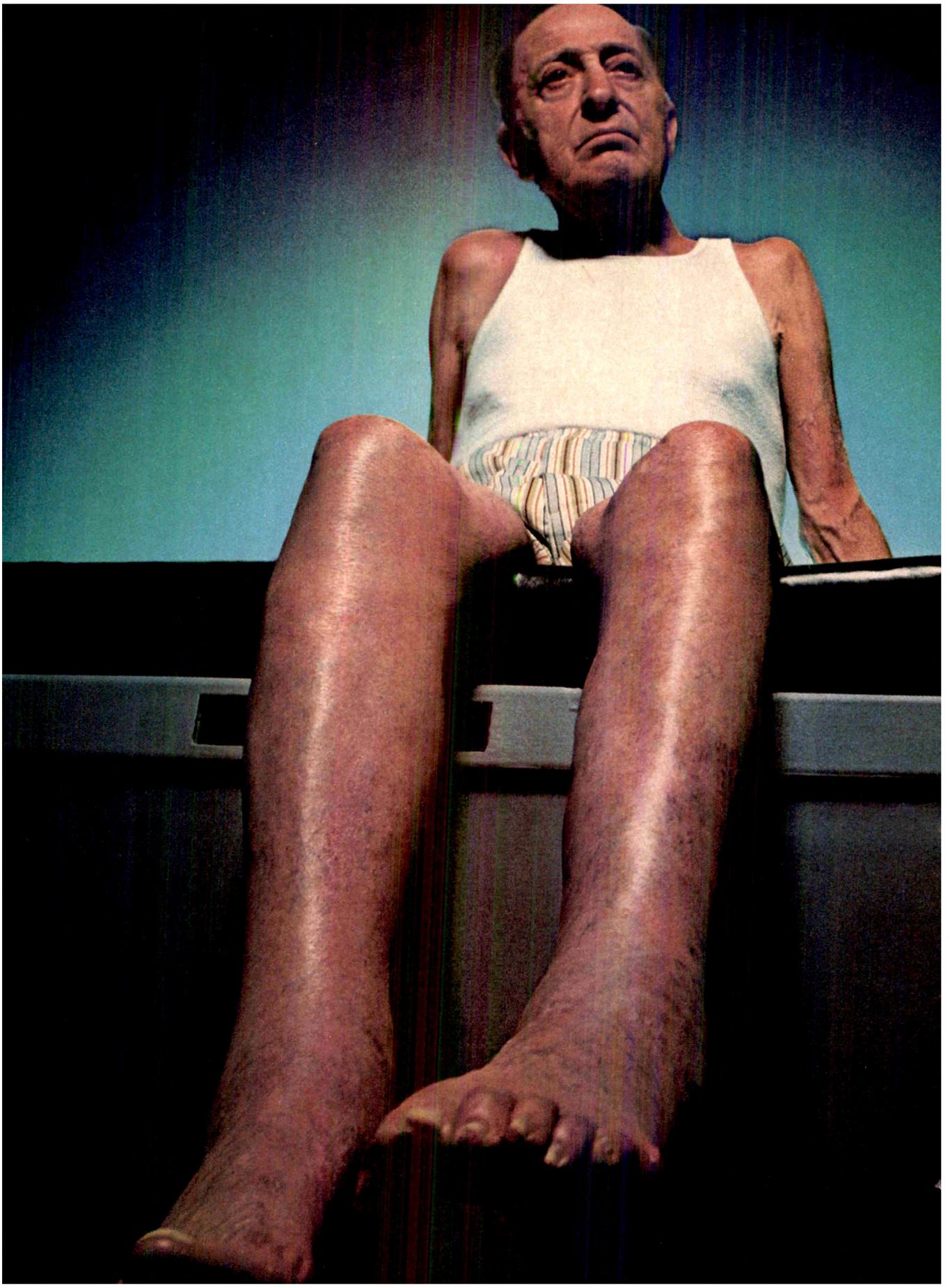
he pacing system may cease to function due to lead-related problems such as splacement, fracture, fibrotic tissue formation and elevated thresholds.

Side Effects

Body rejection phenomena, infection, erosion or migration through body tissue, transvenous lead-related thrombosis, embolism.

How Supplied

Medtronic permanent implantable leads are supplied sterilized and individually wrapped. Medtronic pacing leads are designed to be used with Medtronic pulse generators.



In cardiac edema...
the diuretic most likely to succeed.

It can outperform the thiazides in sodium loss

Lasix® (furosemide) has a greater potential for ridding the body of excess sodium and water than any other commonly used diuretic. A potential that has been realized in multiple comparative studies in patients with cardiac edema.

That's why Lasix is the diuretic most likely to succeed in all degrees of cardiac edema.

It need not go beyond them in potassium loss

With Lasix, the key to minimizing electrolyte disturbances is proper dosage. For if you control the cardiac patient's urine output and edema by titrating the dosage, the result likely will be excretion of less potassium because Lasix produces a dilute urine. As with any diuretic, electrolyte depletion can occur during therapy with furosemide. Careful clinical and laboratory observations are recommended.

And it often works where thiazides can't

Unlike other commonly used diuretics, Lasix can be useful in patients with severely depressed renal function. Even in the presence of renal insufficiency with acidosis, alkalosis or hypoalbuminemia, Lasix has been found both effective and well tolerated. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the drug should be discontinued. Lasix is contraindicated in anuria.

The basic unit–
for initial therapy.
40 mg tablets.

The adjuster unit–
for maintenance therapy.
20 mg tablets.

LASIX® (furosemide)

A brief summary of the Prescribing Information for Lasix (furosemide).

WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.

Indications: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs. Patients not adequately controlled with thiazides probably will not be adequately controlled with furosemide.

Contraindications: Because animal reproductive studies have shown that furosemide may cause fetal abnormalities, the drug is contraindicated in women of childbearing potential. Anuria. Continued use if increasing azotemia and oliguria occur during treatment of severe progressive renal disease. Hepatic coma. Electrolyte depletion. History of hypersensitivity to the compound.

Warnings: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Perform frequent serum electrolyte, CO_2 and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. **Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital.** Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions.

Precautions: As with any potent diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Since furosemide potentiates the effect of antihypertensive medications, reduce the dose of these agents when furosemide is administered to edematous hypertensive patients. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Cases of tinnitus and reversible hearing impairment have been reported when parenteral furosemide therapy preceded oral use. There are also reports of irreversible hearing impairment. Usually, ototoxicity has been reported when doses of furosemide exceeding several times the usual recommended dose were injected rapidly in patients with severe impairment of renal function who were also often receiving other drugs known to be ototoxic. If the physician elects to use high dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, it has been reported that an infusion rate not exceeding 4 mg furosemide per minute has been used.) Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Exercise great caution in administering curare or its derivatives to patients undergoing furosemide therapy, and it is advisable to discontinue furosemide for one week prior to any elective surgery.

Adverse Reactions: Various forms of dermatitis, urticaria and rare forms of exfoliative dermatitis, erythema multiforme, pruritus, paresthesia, blurring of vision, postural hypotension, nausea, vomiting, or diarrhea. Anemia, leukopenia, aplastic anemia, and thrombocytopenia (with purpura). Rare cases of agranulocytosis, which responded to treatment. Although relationship to the drug has not been established with certainty, the following rare adverse reactions have been reported: sweet taste, oral and gastric burning, paradoxical swelling, headache, jaundice, thrombophlebitis and emboli, and acute pancreatitis. Furosemide-induced diuresis may be accompanied by weakness, fatigue, light-headedness or dizziness, muscle cramps, thirst, increased perspiration, urinary bladder spasm, and symptoms of urinary frequency.

Q6689J-176

HOECHST-ROUSSEL
PHARMACEUTICALS INCORPORATED
SOMERVILLE, NEW JERSEY 08876

REG TM HOECHST AG

The Oxford Medilog ECG Analysis System.

A total capability in computerized arrhythmia detection and analysis.



Proven up to 98% efficient, rapid, reliable, cost effective

Generation upon generation of instrumentation has been introduced just to catch up with today's techniques in ECG monitoring and analysis. Oxford, meanwhile has always been moving ahead to bring you 'tomorrow's technology today.'

Accurate recording of ECG data is of course vital — but efficient, rapid and accurate analysis of ECG information, presented in the way the cardiologist requires, is paramount. The Oxford Medilog Scanner is a total concept in computerized arrhythmia detection and analysis developed jointly by a team of eminent cardiologists and specialist medical electronics experts.

The scanner rapidly analyses one or two channels of ECG simultaneously. It's also designed with the technician in mind. Push-button operation and clarity of displays for automatic or manual recognition of SVE, VE, S-T levels, R-R interval, histogram and QRS morphology.

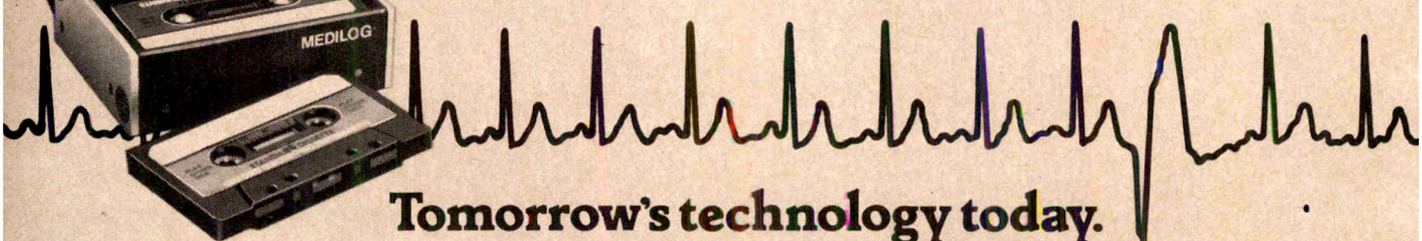
Our system of discrimination against artifact is proven up to 98% efficient — depending on the quality of ECG recording. A unique 60 Hz crystal clock unit eliminates the effect on output data from tape speed variations and tape stretch.

Then there's the Oxford Medilog patient monitor — outstanding in reliability and simplicity. Hook up to the patient, press a single on/off switch and you can collect up to 24 hours of continuous data on 4 independent channels — all on one side of a single C.120 cassette. Completely self-powered, self-contained and weighing less than 1 lb fully loaded, it is worn with a convenient body belt or may even be carried in a pocket. Precise tape speed control is maintained via a 60 Hz crystal clock control system. An event button provides for documentation of syncopol episodes as they occur during recording and also allows instant event recognition during date playback.



For full Oxford Medilog details or a demonstration call Jack Frost, Vice-President, Marketing Operations, on (301) 992 7533 or write to:
Oxford Medilog Inc., 9130-H Red Branch Road, Columbia, Maryland 21045.

OXFORD MEDILOG INC



Tomorrow's technology today.

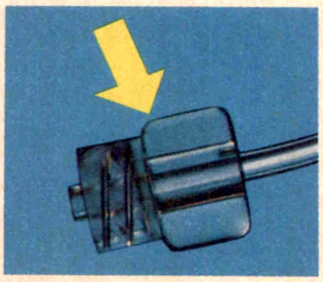


Now! Tygon monitoring lines.
For greater patient safety, greater convenience.

The new Tygon family of monitoring/administration lines brings to the medical profession significant safeguards and conveniences found in no other monitoring lines.

Clarity
From end to end, Tygon monitoring/administration lines are clear. Not only the tubing, but the fittings as well. This offers an important advantage: easier, positive visual checking for air bubbles or other emboli — at a glance.

Controlled Damping
The sturdy Tygon tubing walls assure faithful transmission of pressure without loss, unlike soft-walled tubing.

Integral fittings


The luer lock connectors are **molded** to the tubing, not glued-on. This eliminates the danger of leakage and the possibility of contamination by solvent transfer. Another advantage is the little "wings" on the connectors which permit easy manipulation with gloved hands for fast assembly.

Ready to use, disposable
Each Tygon monitoring/administration line is sterile-packaged in a peel-open pouch and is designed for single patient use.

The name "Tygon" — your best assurance
Tygon® tubing, a product of the Norton Company, has earned a reputation for undeviating excellence in the health care field...particularly where critical procedures are concerned.

Tygon monitoring/administration lines are formulated and produced with this same uncompromising attention to excellence. From raw material to finished product, Norton alone has total manufacturing responsibility. This way, Norton can completely control and maintain the high quality that the medical profession expects from the trusted name "Tygon".



For detailed information on Tygon monitoring/administration lines including sizes, end connector options, and selection data, write for Bulletin MA-1000. Better yet, call Norton toll-free 800-321-9634 (Ohio call collect 216-633-3224).

NORTON HEALTH CARE PRODUCTS
P.O. BOX 350 AKRON, OHIO 44309 TEL: (216) 633-3224

37043A

Introducing the first step-by-step rehabilitation program for the PVD patient



Until now, there has been a gap in the treatment of Peripheral Vascular Disease (PVD). That gap was the lack of a structured program that encouraged therapeutic walking. Many authorities agree that therapeutic walking should be the cornerstone of treatment for PVD patients.

Now, USV Laboratories Inc. introduces the first structured program designed to aid the PVD patient through therapeutic walking.

This program, in the form of a kit available at your request, takes a step-by-step approach to important aspects of PVD management. It also helps gain the patient's active participation in his own treatment.

Step 1. Explanation

The program explains the therapeutic benefits of walking to the patient. It includes a simplified explanation of PVD for the patient and the plan for rehabilitation.

Step 2. Instruction.

With proper walking, the patient can realize maximum therapeutic benefits. Therefore, instruction is included on how to walk properly.

Step 3. Motivation

Aids have been prepared for distribution to the patient in order to involve him in the program. The most important is a log in which the patient records his progress for his own and your review. The patient also receives a summary of the many aspects of the program discussed in your office. This includes instruction on proper walking for practice at home.

How to receive your copy of the PVD rehabilitation program

You can receive this educational and instructional program by contacting your USV representative or by writing to: Walking Program, Medical Department, USV Laboratories Inc., Tuckahoe, N.Y. 10707.

The role of Arlidin (nylidrin HCl) in a walking program

Improved blood flow in skeletal muscles

Arlidin acts specifically to dilate vessels in skeletal muscles, such as the calf.

Maintenance of mean arterial pressure

Arlidin maximizes delivery of blood to ischemic areas and minimizes risk of hypotensive episodes.

Relief of symptoms of ischemia associated with PVD *

Symptomatic improvement can enhance the patient's ability to function and to comply with a recommended walking program.

Brief Summary

***Indications:** Based on a review of this drug by the National Academy of Sciences – National Research Council and/or other information, FDA has classified this drug as "possibly" effective for peripheral vascular disease and circulatory disturbances of the inner ear. Final classification of the less-than-effective indications requires further investigation.

Contraindications: Acute myocardial infarction, paroxysmal tachycardia, progressive angina pectoris and thyrotoxicosis. **Warnings:** In patients with cardiac disease such as tachyarrhythmias and uncompensated congestive heart failure, the benefit/risk ratio should be weighed prior to therapy and reconsidered at intervals during treatment. **Adverse Reactions:** Trembling, nervousness, weakness, dizziness (not associated with labyrinthine artery insufficiency), palpitations, nausea and vomiting may occur. Postural hypotension, while not reported, may also occur. **Dosage:** Orally, 3 to 12 mg. three or four times a day. **How Supplied:** White, scored tablets, 6 mg. and 12 mg. Bottles of 100 and 1000; single-dose blister packs, boxes of 100 (10 x 10 strips).



The rehabilitation program

Walking & Arlidin® (nylidrin HCl)

USV LABORATORIES

USV Laboratories Inc.
Manati, P.R. 00701

New wide-angle probe for EkoSector I.™



It gives you the big picture.

Our remarkable new wide-angle probe gives you an enlarged cross-sectional scan of the heart, making it easier for you to visualize and correlate relative position and motion patterns of intracardiac structures for a more accurate diagnosis.

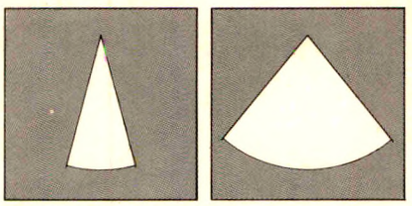
In addition this new probe provides an image of extremely high resolution.

More innovation without obsolescence.

The new wide-angle probe is yet another SKI innovation designed to protect your original investment while providing extra value to you.

If you already own an EkoSector I™, a modification will enable you to use the standard probe and the new wide-angle probe interchangeably. Both heads simply attach to the existing probe handle.





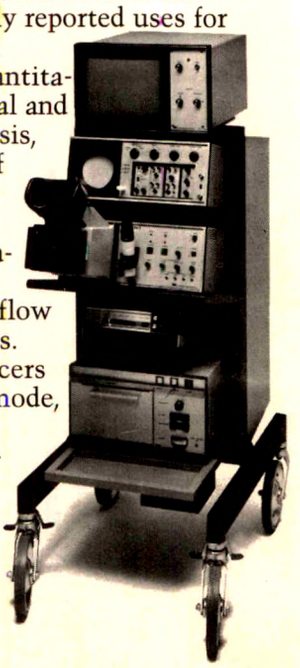
The new wide-angle probe displays a scan that is 50° greater than the standard 30° probe. Both probes will be supplied with all new EkoSector I units. The wide-angle probe is supplied for existing systems as an optional accessory.

Real-time cross-sectional scanning and unique design.

The SKI patented direct processing method provides distortion-free electronic images and correct, spatially-oriented, information concerning the depth relative to the chest wall, and real-time motion of cardiac structures.

Clinically reported uses for EkoSector I include quantitation of mitral and aortic stenosis, detection of ventricular aneurysms and localization of ventricular outflow obstructions.

Transducers provide A-mode, M-mode or sector scanning of the heart or other organs. Images can be displayed on the oscilloscope or on the large external X-Y monitor. A videotape recorder allows recording of M-mode or cross-sectional scans along with verbal comments. Playback can be at normal speed, slow motion or stop-frame projection. Recorded images can be selectively altered in size by means of the tissue depth control.



If you already own an Ekoline 20A, the EkoSector I can easily be interfaced with it, cutting your cost for the whole system by almost half. Even if you do not already own an Ekoline 20A, the complete system still costs less than competing systems.

SmithKline Instruments, Inc.

880 West Maude Avenue, Sunnyvale CA. 94086 (408) 732-6000

Please send me more information on the new EkoSector I ☐ Ekoline 20A ☐

Name _____

Hospital _____

Address _____

City _____

State _____ *Zip* _____

Mail to Smith Kline Instruments, Inc. P.O. Box 1947, Sunnyvale, California 94086

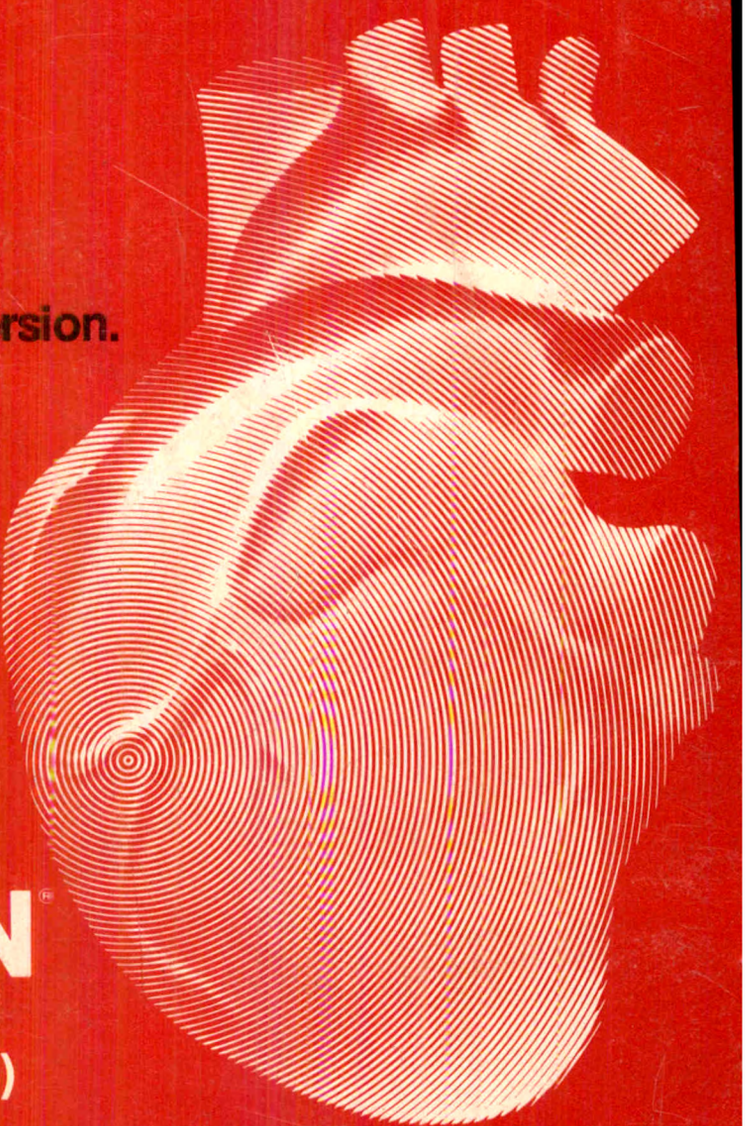
Or, call 800-538-1556 toll free. In California call collect 408-732-6000.

AJC

In Canada, mail to Smith Kline Instruments, 300 Laurentien Blvd., St. Laurent, Quebec, Canada. In the United Kingdom, mail to Smith Kline Instrument Co. Ltd., Welwyn Garden City, Hertfordshire, England.

SKI
a SmithKline company

The Pacekeeper™



For ventricular arrhythmias.
For atrial arrhythmias.
For smooth, trouble-free conversion.
For steady maintenance.

CARDIOQUIN®
TABLETS
(quinidine polygalacturonate)

- ☐ Greater GI tolerance than with quinidine sulfate
- ☐ Full quinidine cardiodynamics
- ☐ Convenient b.i.d. or t.i.d. dosage for most patients

CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm —whether with CARDIOQUIN Tablets or electroconversion— only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases. The polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 50.

Purdue Frederick

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MAY 22, 1978

The American Journal of CARDIOLOGY®

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Symposium on New Aspects of Antiarrhythmic Therapy

Douglas P. Zipes, MD, FACC, Guest Editor

Contents on Page A5

A YORKE MEDICAL JOURNAL

logical therapy for the vast
who need more or other



Logical therapy because essential hypertension is usually characterized by elevated peripheral resistance with normal cardiac output. ALDOMET lowers blood pressure apparently by lowering peripheral resistance—while cardiac output is usually maintained.

Appropriate for all degrees of hypertension when drug therapy is required

Highly effective in mild, moderate, or severe hypertension, ALDOMET (Methyldopa, MSD) is useful when there has been an inadequate response to initial thiazide therapy, or as initial therapy when thiazides are deemed inappropriate or contraindicated (for example, when hypersensitivity to sulfonamide-derived drugs exists).

Appropriate for many hypertensive patients requiring special consideration

- hypertensive patients with renal impairment—ALDOMET usually does not reduce glomerular filtration rate, renal blood flow, or filtration fraction. (Methyldopa is largely excreted by the kidney, and patients with impaired renal function may respond to smaller doses.)
- hypertensive children requiring drug therapy (See pediatric dosage recommendations in the addendum on the last page of this advertisement.)

Not contraindicated in the following coexisting conditions in which some other antihypertensives are contraindicated

- congestive heart failure (Edema may occur with ALDOMET. This is usually relieved by the use of a diuretic, but if edema progresses methyldopa should be discontinued.)
- coronary artery disease (Aggravation of angina pectoris may occur with ALDOMET.)
- mitral valvular rheumatic heart disease
- bronchial asthma
- allergic rhinitis during the pollen season
- greater than first-degree heart block
- active peptic ulcer
- ulcerative colitis

majority of hypertensives
therapy than a thiazide...



Therapeutic limitations

ALDOMET is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previous methyldopa therapy has been associated with liver disorders.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, please see the brief summary of prescribing information.

NATIONAL HIGH BLOOD PRESSURE MONTH
MAY 1978

TABLETS: 500 mg, 250 mg, and 125 mg

ALDOMET®
(METHYLDOPA | MSD)

MSD
MERCK SHARP & DOHME

For a brief summary of prescribing information, please see following page.

TABLETS: 500 mg, 250 mg, and 125 mg

ALDOMET®
(METHYLDOPA | MSD)

Logical therapy for the vast majority of hypertensives who need more or other therapy than a thiazide

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor.

Allergic: Drug-related fever, lupus-like syndrome, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 500.

For more detailed information, consult your MSD representative or see full prescribing information.

Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

J8AM17(709)

addendum

MSD
MERCK SHARP & DOHME

DOSAGE INFORMATION ON ALDOMET® (Methyldopa | MSD)

Adults

initiating therapy

- 250 mg b.i.d. or t.i.d. the first 48 hours
- increase or decrease, preferably at intervals of not less than two days, until response is adequate
- start dosage increases in the evening to minimize sedation
- adjusting dosage may prevent morning hypotension without losing control of afternoon blood pressure
- when ALDOMET is added, the dosage of thiazides need not be changed
- when given with antihypertensives other than thiazides, the dose of these agents may have to be adjusted and the starting dosage of ALDOMET should be limited to 500 mg daily in divided doses

maintaining therapy

- usually 500 mg to 2.0 g daily in two to four doses
- maximum recommended daily dose is 3.0 g
- if effective control of blood pressure cannot be maintained on 2.0 g methyldopa daily and a thiazide is not already part of the regimen, a thiazide should be added
- occasional tolerance may occur, usually between the second and third month of therapy; adding a diuretic or increasing the dosage of ALDOMET frequently restores effective control
- patients with impaired renal function may respond to lower doses; syncope in older patients may be related to an increased sensitivity and advanced arteriosclerotic vascular disease and may be avoided by lower doses

Children

- initial dosage is based on 10 mg/kg of body weight daily in two to four doses
- increase or decrease daily dosage until adequate response is achieved
- maximum dosage is 65 mg/kg or 3.0 g daily, whichever is less

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NOTE: Depending upon the response desired, the dosage may need to be varied and the blood level and/or electrocardiographic response closely monitored during initial treatment.

Contraindications: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.

Partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. Renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects; ventricular premature beats, ventricular tachycardia or flutter while on the drug. Marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis. Idiosyncrasy or hypersensitivity to quinidine.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate.

Precautions: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy.

Quinidine in large doses may reduce the contractile force of the heart; therefore, extreme caution should be exercised in using the drug in patients with severe heart disease, hypotension or digitalis intoxication.

It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

Adverse Reactions: Cinchonism, tinnitus, decreased auditory acuity, vertigo, headache, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis, hypotension, respiratory distress, and gastrointestinal disturbances.

101-48R

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975 Introduction: Miles To Go

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979 Roles of Psychologic Stress and Autonomic Nervous System Changes in Provocation of Ventricular Premature Complexes

BERNARD LOWN and REGIS A. DeSILVA, *with the technical assistance of* RICHARD LENSON

Psychologic stress testing using performance of mental arithmetic, reading from colored cards and recounting emotionally charged experiences induced a significant increase in ventricular premature beat frequency in 11 of 19 patients with a history of advanced grades of ventricular arrhythmias. Elicitation of vagal or sympathetic autonomic reflexes in 14 of these 19 subjects induced a significant arrhythmia in only 1 patient, thus suggesting that such reflexes are insufficient to trigger enhanced ventricular ectopic activity. Input from higher nervous centers may be a necessary element in providing the type of neural traffic that disorganizes cardiac rhythm. The physician managing patients with recurrent life-threatening arrhythmias must be attentive to the psychophysiologic variables that may play a part in the genesis of this disorder.

986 Pharmacokinetics of Antiarrhythmic Drugs

RAYMOND L. WOOSLEY and DAVID G. SHAND

This review describes the basic principles of simple pharmacokinetics of the most commonly used antiarrhythmic drugs (lidocaine, procainamide, quinidine, disopyramide, phenytoin and propranolol) and their application in the management of patients with arrhythmias. Kinetics can be used as a guide only to initial therapy; thereafter, drug dosage must be adjusted according to clinical outcome. The most important facet of the kinetics of the antiarrhythmic drugs is that the variation in plasma levels achieved with any given dosage regimen often varies much more than the therapeutic range of desirable concentrations. Average doses are used as an approximation and should be reduced in patients with renal or hepatic failure. A 30 to 50 percent reduction in dosage is wise in patients with obvious heart failure. Thereafter, the dose should be titrated to achieve the desired effect without signs of toxicity or side effects. The ability of other drugs and electrolyte changes, particularly in serum potassium, to alter the effects of antiarrhythmic agents requires that these factors also be considered in establishing optimal therapy.

996 Contribution of Ambulatory Electrocardiographic Monitoring to Antiarrhythmic Management

DONALD C. HARRISON, JOHN W. FITZGERALD and ROGER A. WINKLE

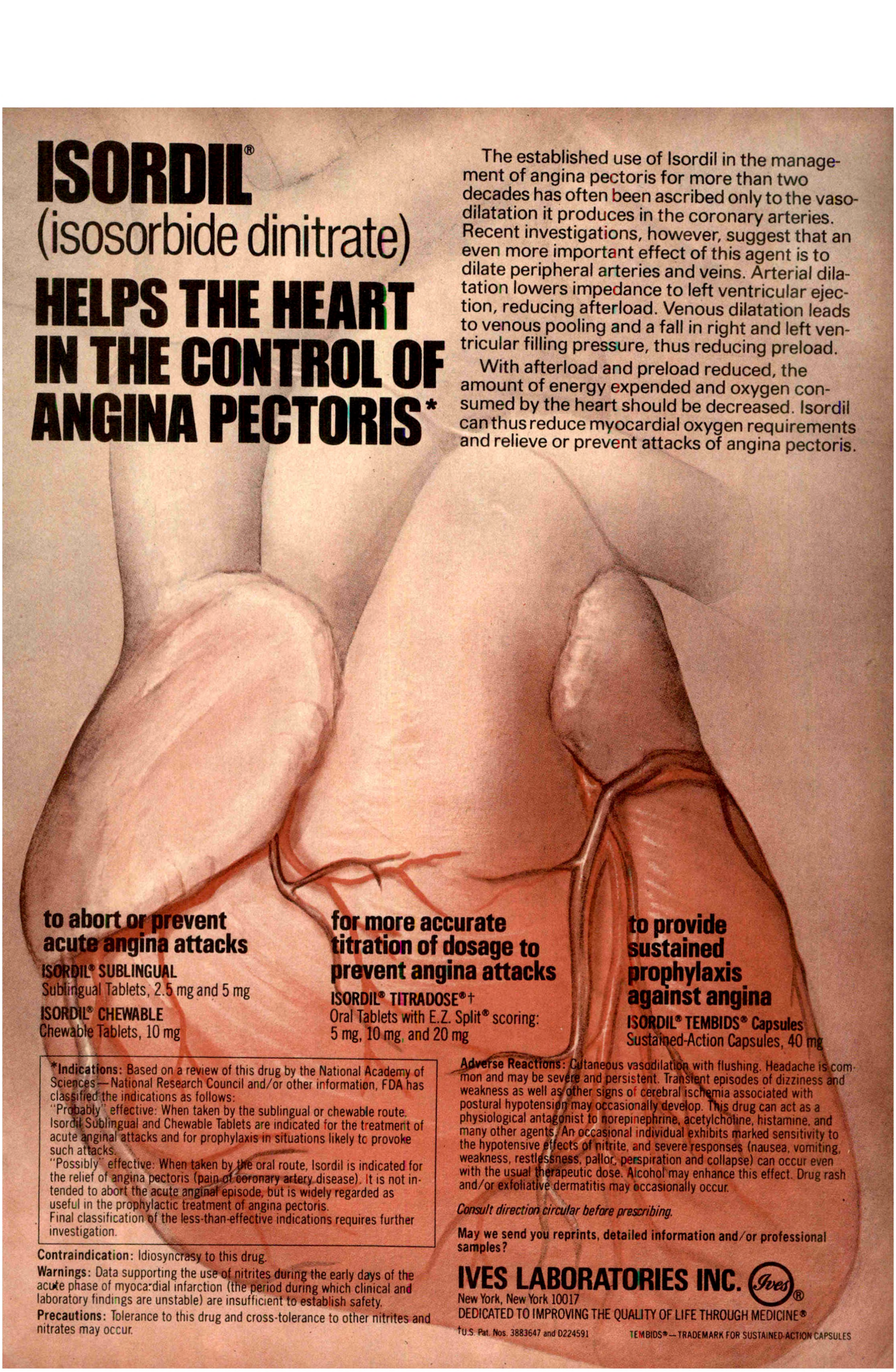
Ambulatory electrocardiographic monitoring has three potential uses: (1) to detect cardiac arrhythmias, (2) to provide prognostic information about the arrhythmia and need for therapy, and (3) to evaluate the effectiveness of drug therapy. Such monitoring reveals that apparently normal subjects may experience a wide range of cardiac rhythm and conduction disturbances, especially as the age of the population being monitored increases. Antiarrhythmic drug therapy should not be initiated for arrhythmias without known clinical significance. In patients with coronary artery disease, ambulatory monitoring can identify those with frequent complex ventricular arrhythmias who are at risk of sudden cardiac death. Such monitoring can document the effectiveness of antiarrhythmic drug therapy for ventricular irritability and define the dosage regimens and plasma concentrations effective for most patients.

Continued on page A13

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"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Consult direction circular before prescribing.

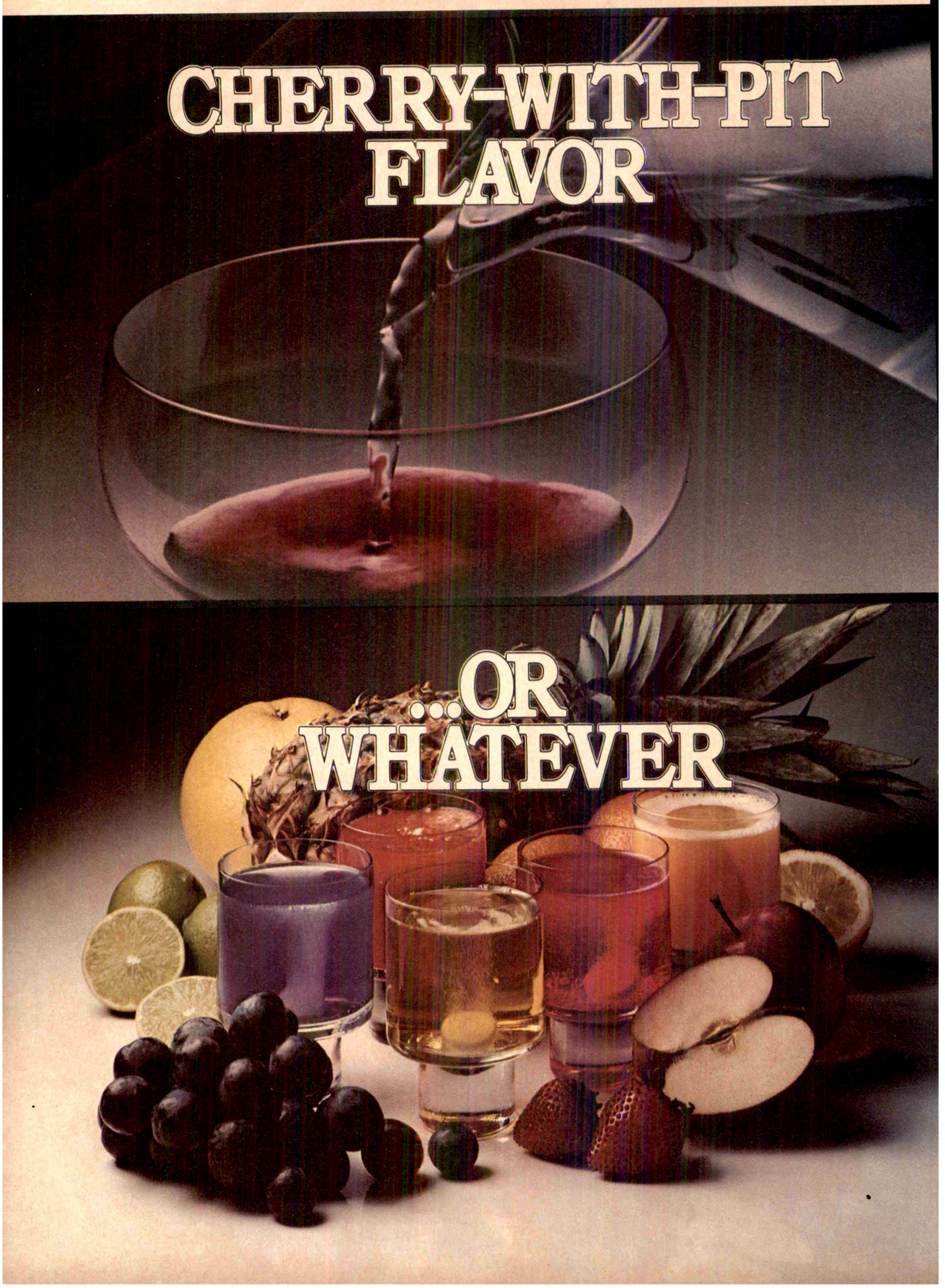
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Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

Indications: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

Contraindications: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements.

Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis.

High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest.

To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve each Klorvess Effervescent Tablet in 3 to 4 ounces of water or fruit juice, or dilute each tablespoonful of Klorvess (potassium chloride) 10% Liquid in 3 to 4 ounces of water. Both of these solutions should be ingested slowly with or immediately after meals.

Adverse Reactions: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts.

The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest.

The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

Dosage and Administration: Klorvess Effervescent Tablets: Adults—One Klorvess Effervescent Tablet (20 mEq each of potassium and chloride) completely dissolved in 3 to 4 ounces of cold water or fruit juice 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) of Klorvess Liquid (20 mEq of potassium chloride) completely diluted in 3 to 4 ounces of water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating. Deviations from these recommended dosages may be indicated in certain cases of hypokalemia based upon the patient's status. The average total daily dosage must be governed by the patient's response as determined by frequent evaluation of serum electrolytes, EKG and clinical status.

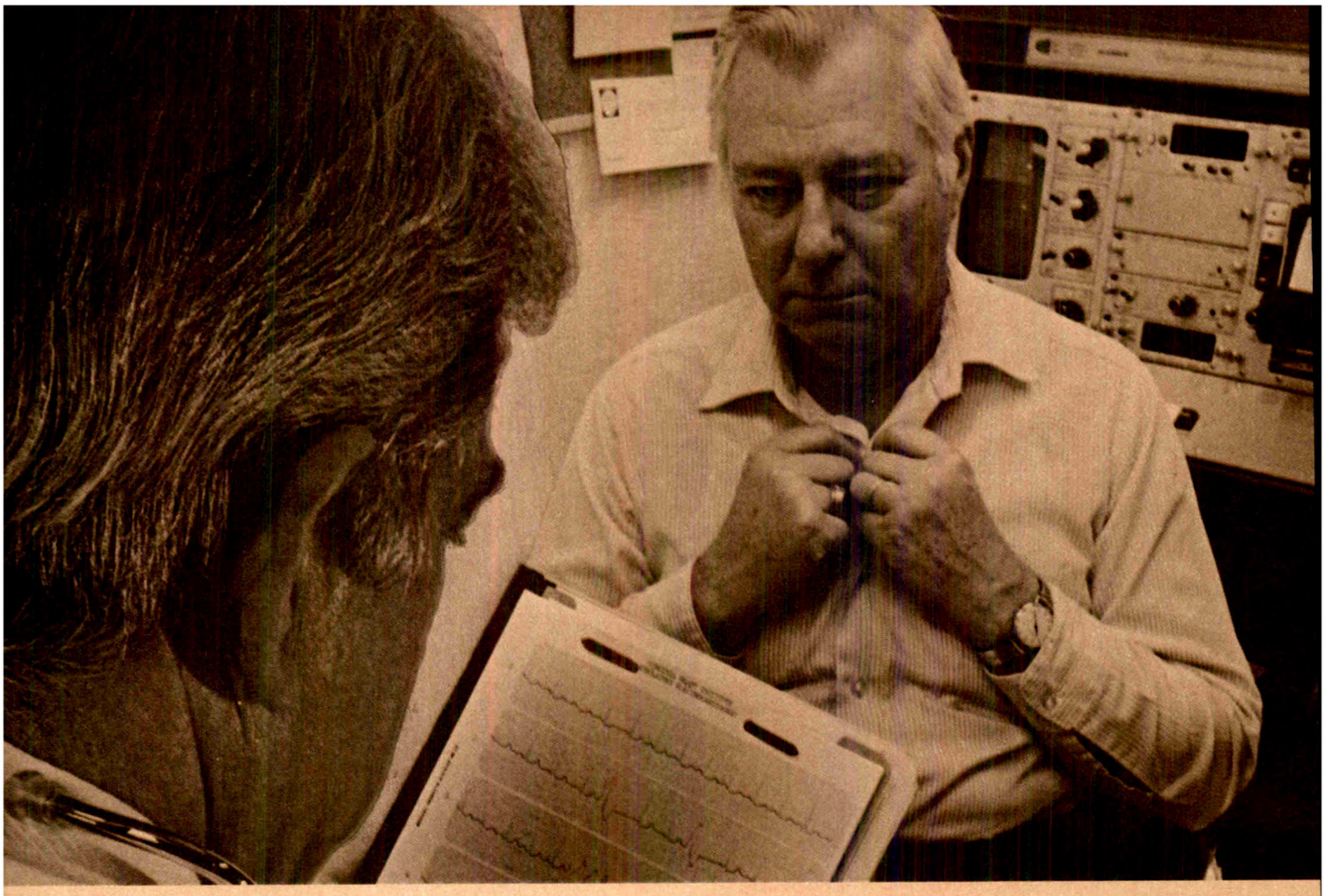
Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

Treatment of Hyperkalemia: 1. Dextrose solution, 10 or 25% containing 10 units of crystalline insulin per 20 g dextrose, given IV in a dose of 300 to 500 ml in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resins, orally and as retention enema. (Caution: Ammonium compounds should not be used in patients with hepatic cirrhosis.) 3. Hemodialysis and peritoneal dialysis. 4. The use of potassium-containing foods or medicaments must be eliminated. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

How Supplied: Klorvess Effervescent Tablets (white)—60 tablets (2 Rx units of 30 effervescent tablets each). Each tablet is individually foil wrapped. Klorvess (potassium chloride) 10% Liquid (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Tablets and Liquid are also available in institutional packaging as follows: Klorvess Tablets—30 and 1000 tablets; Klorvess Liquid—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

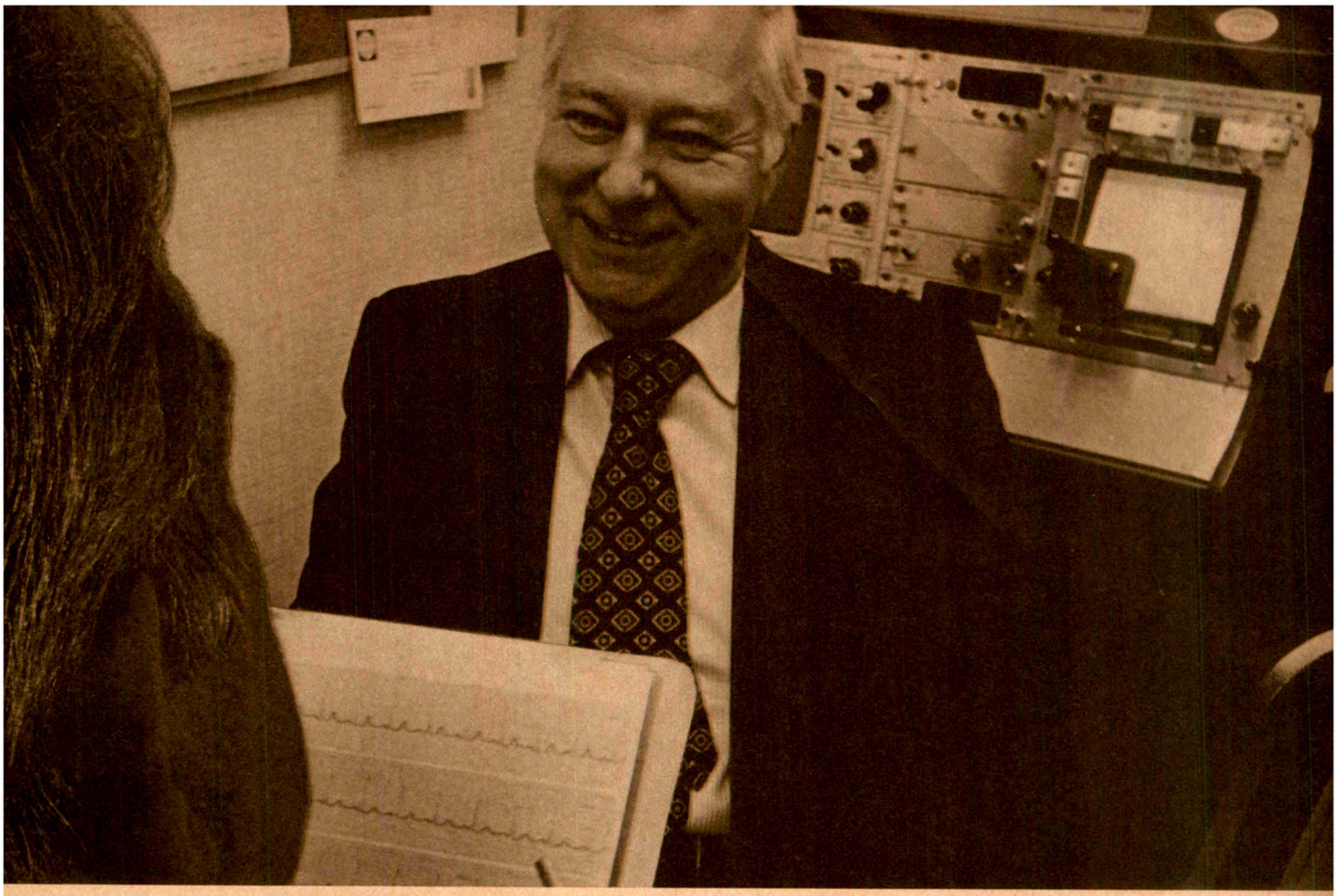
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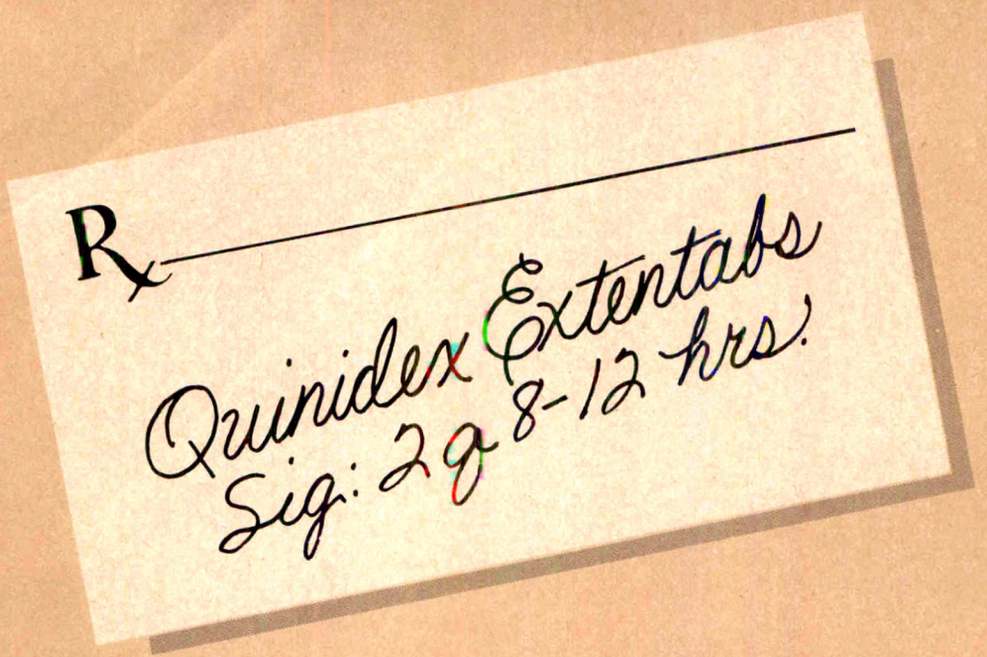
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1005 New Antiarrhythmic Agents. Amiodarone, Aprindine, Disopyramide, Ethmozin, Mexiletine, Tocainide, Verapamil

DOUGLAS P. ZIPES and PAUL J. TROUP

This review of new antiarrhythmic agents summarizes the present status, clinical experience, side effects, clinical pharmacology and electrophysiologic actions of amiodarone, aprindine, disopyramide, ethmozin, mexiletine, tocainide and verapamil. Each appears to be a promising candidate for approved clinical use in the United States, and disopyramide (Norpace) has already been approved. Although pacing and surgical ablation techniques have resulted in spectacular successes for some patients with certain types of drug-resistant tachyarrhythmias, most patients must be treated medically because of the large number with symptomatic and even life-threatening cardiac arrhythmias. As more effective antiarrhythmic agents with fewer side effects are developed, the need for pacing and surgical approaches will diminish.

1025 Electrical Management of Arrhythmias With Emphasis on the Tachycardias

HEIN J. J. WELLENS, FRITS W. BÄR, ANTON P. GORGELS and JERONIMO FARRÉ MUNCHARAZ

This review describes in detail the use of cardiac pacing in the short- and long-term management of patients suffering from tachycardias. Suppression of arrhythmias by increasing heart rate with pacing depends not only on reaching a critical heart rate but sometimes also on the pattern of cardiac activation after the paced impulse. The use of appropriately timed stimuli may terminate tachycardia in patients with tachycardia due to a reentry mechanism. "Overdrive" pacing in patients with abnormal automaticity may cause temporary slowing or cessation of tachycardia but not in long-lasting termination. Atrial flutter is the most suitable type of tachycardia for treatment with temporary pacing. Stimulation can be most successfully performed low in the atrium, using gradually increasing pacing rates and stimulus strength. In patients seriously handicapped by tachycardia uncontrolled with drug treatment, the following modes of pacing are available for chronic treatment: (1) the single stimulus method ("underdrive" pacing), (2) "overdrive" pacing, and (3) sequential pacing. Orthorhythmic and scanning pacemakers are still too complicated, expensive and vulnerable to failure for long-term use in implantable form.

1035 Surgical Treatment of Arrhythmias: Current Status and Future Directions

JOHN J. GALLAGHER

This review of currently available surgical techniques for modifying or ablating rhythm disturbances includes data on procedures relating to (1) supraventricular and junctional tachyarrhythmias, (2) ventricular arrhythmias, and (3) arrhythmias associated with the preexcitation syndrome. These therapeutic surgical alternatives include ablation of the site of origin of arrhythmias (excision or destruction in situ) or modification of the milieu of the site of origin (autonomic manipulation, revascularization and other measures). Design of a surgical procedure for more effective treatment of ventricular and other arrhythmias requires greater understanding of the underlying mechanism and refinement of the ability to localize precisely the site of origin of these arrhythmias.

CLINICAL STUDIES

1045 Clinical, Electrocardiographic and Electrophysiologic Observations in Patients With Paroxysmal Supraventricular Tachycardia

DELON WU, PABLO DENES, FERNANDO AMAT-Y-LEON, RAMESH DHINGRA, CHRISTOPHER R. C. WYNDHAM, ROBERT BAUERNFEIND, PERVAIZE LATIF and KENNETH M. ROSEN

Electrophysiologic studies in 79 patients with documented paroxysmal supraventricular tachycardia and no ventricular preexcitation suggested atrioventricular (A-V) nodal reentrance in 50, reentrance utilizing a concealed extranodal pathway in 9, sinus or atrial reentrance in 7 and ectopic automatic tachycardia in 3. Selected clinical characteristics in the three largest groups are analyzed, compared and discussed. In approximately 90 percent of the patients with recurrent spontaneous paroxysmal supraventricular tachycardia, the arrhythmia could be reproduced in the cardiac catheterization laboratory. In addition, in most of the patients, a specific mechanism could be defined with atrial and ventricular stimulation techniques. The most common mechanism of paroxysmal supraventricular tachycardia appears to be A-V nodal reentrance, although other mechanisms are not infrequent.

1052 Electrophysiologic Characteristics of Concealed Bypass Tracts: Clinical and Electrocardiographic Correlates

ARDESHIR FARSHIDI, MARK E. JOSEPHSON and LEONARD N. HOROWITZ

Left-sided atrioventricular (A-V) bypass tracts functioning as the retrograde limb of the reentrant circuit were found in 12 of 60 consecutively studied patients undergoing electrophysiologic study for supraventricular tachycardia. When compared with supraventricular tachycardia due to A-V nodal reentry, clinical findings suggestive of a concealed bypass tract included: (1) P wave following the QRS complex, (2) negative P wave in lead I during

Continued on page A14

the tachycardia, and (3) bundle branch block aberration during the tachycardia. Other characteristics included shorter cycle lengths of tachycardia, younger patient age and lesser incidence of organic heart disease. As newer specific antiarrhythmic drugs become available and surgical therapy of refractory supraventricular tachycardia becomes established, the diagnosis of supraventricular tachycardia utilizing a concealed bypass tract will assume greater significance.

1061 Effects of Propranolol on Anomalous Pathway Refractoriness and Circus Movement Tachycardias in Patients With Preexcitation

PABLO DENES, JAMES M. CUMMINGS, ROSS SIMPSON, DELON WU, FERNANDO AMAT-Y-LEON, RAMESH DHINGRA and KENNETH M. ROSEN

Although propranolol is frequently recommended for management of tachycardias complicating the Wolff-Parkinson-White syndrome, this electrophysiologic study in 18 patients shows it has an insignificant effect on anterograde and retrograde anomalous pathway properties and in most cases does not interfere with induction of sustained circus movement tachycardia. It does slow slightly the rate of tachycardia and, in a minority of cases, it inhibits induction of sustained paroxysmal supraventricular tachycardia by increasing atrioventricular nodal refractoriness. Because propranolol does not affect anterograde anomalous pathway refractoriness, this drug would probably not slow ventricular rates during atrial fibrillation in patients with preexcitation, and in these patients its negative inotropic effect may prove deleterious.

1068 Multiple Intracardiac Recordings in Evaluation of Patterns Occurring During Attempted His Bundle Pacing in Man

IVAN J. MENDOZA, RUEY J. SUNG, STEPHEN M. MALLON, AGUSTIN CASTELLANOS and ROBERT J. MYERBURG

Use of the multiple catheter technique permits the categorization of the QRS configuration due to His bundle pacing, right septal pacing and (some) fusion beats resulting from combined His and right septal pacing. In spite of certain limitations, data obtained by this method can enhance the comprehension of the various QRS patterns and activation sequences occurring during attempted His bundle pacing in the human heart. As shown in this study of 30 patients, electrophysiologic His bundle pacing was characterized by a QRS complex and stimulus (St)-V, St-RVA and St-LV intervals that equaled the QRS configuration, H-V, H-RVA and H-LV intervals of sinus beats. Right septal pacing produced a pattern of "complete" left bundle branch block (with normal electrical axis) associated with St-V intervals of 0 msec and St-RVA and St-LV intervals of a different duration from that of the H-RVA and H-LV intervals recorded during sinus rhythm. Fusion QRS configuration depended on the type of ventricular complex present during sinus rhythm.

EXPERIMENTAL STUDIES

1075 Pharmacologic and Behavioral Effects on Arrhythmias That Immediately Follow Abrupt Coronary Occlusion: A Canine Model of Sudden Coronary Death

JON ROSENFELD, MICHAEL R. ROSEN and BRIAN F. HOFFMAN

Occlusion of a major artery by an implanted balloon occluder in a chronically instrumented conscious dog caused single or multiple premature ventricular depolarization, runs of ventricular premature depolarizations or ventricular fibrillation. Latency (time from the onset of occlusion to the onset of the arrhythmia) increased with successive occlusions in the same environment until no arrhythmia occurred during an occlusion of 5.5 minutes. In this state the addition of behavioral stress usually led to recurrence of the arrhythmia. Stress decreased latency and increased the grade of severity of the arrhythmia. Tolamolol (a beta adrenergic blocking agent) increased latency and tended to decrease grade. Both diazepam and tolamolol delayed the onset and reduced the severity of the arrhythmias after stress. The severity of the arrhythmia was inversely related to latency, and latency decreased with increases in heart rate.

1083 Relation Between Ventricular Refractoriness and Regional Myocardial Blood Flow After Acute Coronary Occlusion

WILLIAM P. BATSFORD, DAVID S. CANNOM and BARRY L. ZARET

This study in dogs relating the degree of change in measured ventricular refractory period with the degree of regional myocardial blood flow abnormality after coronary occlusion shows that refractory periods are significantly shortened when regional myocardial blood flow is less than 70 percent of that of nonischemic areas. The greatest change in refractory periods occurs in areas with a regional myocardial blood flow 21 to 40 percent of that of nonischemic areas. Potential sites of origin of ventricular arrhythmias may be dependent on and predictable from regional myocardial blood flow. These results provide a basis for assessing the dependence on regional myocardial blood flow for therapeutic effectiveness of antiarrhythmic agents and for assessing the electrophysiologic effects of interventions directed at salvaging ischemic myocardium.

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METHODS

1089 Catheter Recording of Bachmann's Bundle Activation From the Right Pulmonary Artery: A New Technique for Atrial Mapping and the Study of Supraventricular Tachycardia

SATOSHI OGAWA, LEONARD S. DREIFUS, JAMES G. KITCHEN III, PRAKASH N. SHENOY and MARY JANE OSMICK

These studies in dogs and in four patients indicate that it is possible to record from the proximal right pulmonary artery electrograms of good quality that reflect activation from the region of Bachmann's bundle, identify the precise mechanism of supraventricular tachycardia and evaluate interatrial conduction. Recording of Bachmann's bundle activation is necessary in localizing the precise site of reentry during supraventricular tachycardia. The right pulmonary arterial electrogram can also separate interatrial conduction time from left intraatrial conduction time.

PEDIATRIC CARDIOLOGY

1097 Natural History of Wolff-Parkinson-White Syndrome Discovered in Infancy

MICHAEL E. MANTAKAS, CAROLYN M. McCUE and WILLIAM W. MILLER

Among 20 infants found to have a Wolff-Parkinson-White syndrome before age 1 year and followed up from 1 to 19 years, episodes of supraventricular tachycardia occurred in 90 percent. Associated cardiac defects were present in one third of the patients. Categorizing patients into groups according to the width of the QRS complex and the presence or absence of the delta wave during tachycardia helped in understanding and planning therapy. Eighteen patients had a stable or improved course with growth, but two patients with tetralogy of Fallot died postoperatively with resistant supraventricular tachycardia. Invasive electrophysiologic studies are indicated in symptomatic children older than 1 year and in all infants and children considered for cardiac surgery. All patients with Wolff-Parkinson-White syndrome should have temporary pacing electrodes implanted at operation. Preoperative planning for overdriving any postoperative arrhythmia is essential.

1104 Electrophysiologic Studies After Mustard's Operation for d-Transposition of the Great Vessels

MICHAEL G. SAALOUKE, JORGE RIOS, LOWELL W. PERRY, STEPHEN R. SHAPIRO and LEWIS P. SCOTT

These electrophysiologic studies performed in 16 patients after Mustard's intraatrial baffle operation for d-transposition of the great vessels indicate that a diseased sinus node and interrupted atrial pathways are involved in the genesis of arrhythmias after this operation. Adequate evaluation of arrhythmias in such patients requires not only the standard electrocardiogram but also a 24 hour Holter monitor, His bundle electrograms and determination of sinus nodal recovery time and atrial and atrioventricular (A-V) nodal effective refractory period. Sixty-three percent of the patients had abnormal sinus nodal recovery time. Atrial effective refractory period was prolonged in 4 of the 12 patients in whom it was measured. Previously undetected arrhythmias were found in all patients when the 24 hour Holter electrocardiogram was compared with the standard electrocardiogram. Atropine shortened the sinus nodal recovery time, atrial effective refractory period and A-V nodal effective refractory period in all patients studied.

DIAGNOSTIC SHELF

1110 Second Degree His-Purkinje Block During His Bundle Pacing

AGUSTIN CASTELLANOS, FEDERICO MOLEIRO, RUEY J. SUNG and ROBERT J. MYERBURG

This 62 year old woman with intermittent Wolff-Parkinson-White syndrome, "complete" right bundle branch block and advanced atrioventricular (A-V) block in both (normal and accessory) pathways showed second degree H-V block (2:1 and Wenckebach) when the high right atrium and the His bundle were stimulated at similar cycle lengths. The conduction disturbance occurred in the low His bundle or in the left bundle branch. This is the first report clearly documenting such disturbances during His bundle pacing.

CASE REPORTS

1115 Atrioventricular Nodal Gap Conduction as a Manifestation of Dual Nodal Pathways

DAVID M. MIRVIS and JACK P. BANDURA

Electrophysiologic studies in a 76 year old man with sinus bradycardia showed type I or atrioventricular (A-V) nodal gap conduction physiologically related to conversion from a rapid to a slow A-V nodal conduction mode. Type I or A-V nodal gap may be considered an electrophysiologic consequence of dual A-V nodal pathways. The occurrence of dual A-V conduction paths may not be an uncommon substrate for the recording of A-V nodal gap conduction patterns.

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1119 Self-Initiated Conversion of Paroxysmal Atrial Flutter Utilizing a Radio-Frequency Pacemaker

CHRISTOPHER R. WYNDHAM, DELON WU, PABLO DENES, DANIEL SUGARMAN, SIDNEY LEVITSKY and KENNETH M. ROSEN

Self-initiated rapid atrial pacing utilizing a radio-frequency pacemaker controlled incapacitating recurrent paroxysmal atrial flutter in a 55 year old man when other medical measures failed. Electrophysiologic studies demonstrated that rapid atrial stimulation at rates of 375 to 400/min could induce the flutter and at higher rates of 400 to 460/min could convert the flutter to atrial fibrillation, which later reverted to sinus rhythm. Although the system functioned well from the time of implantation, additional pharmacologic therapy with propranolol and procainamide was needed to achieve clinically satisfactory control of the arrhythmia. Such permanent pacing therapy is appropriate only when previous extensive trial has shown that the arrhythmia is resistant to several appropriate drugs, singly or in combination, or that drug toxicity has prevented pharmacologic control.

EDITORIALS

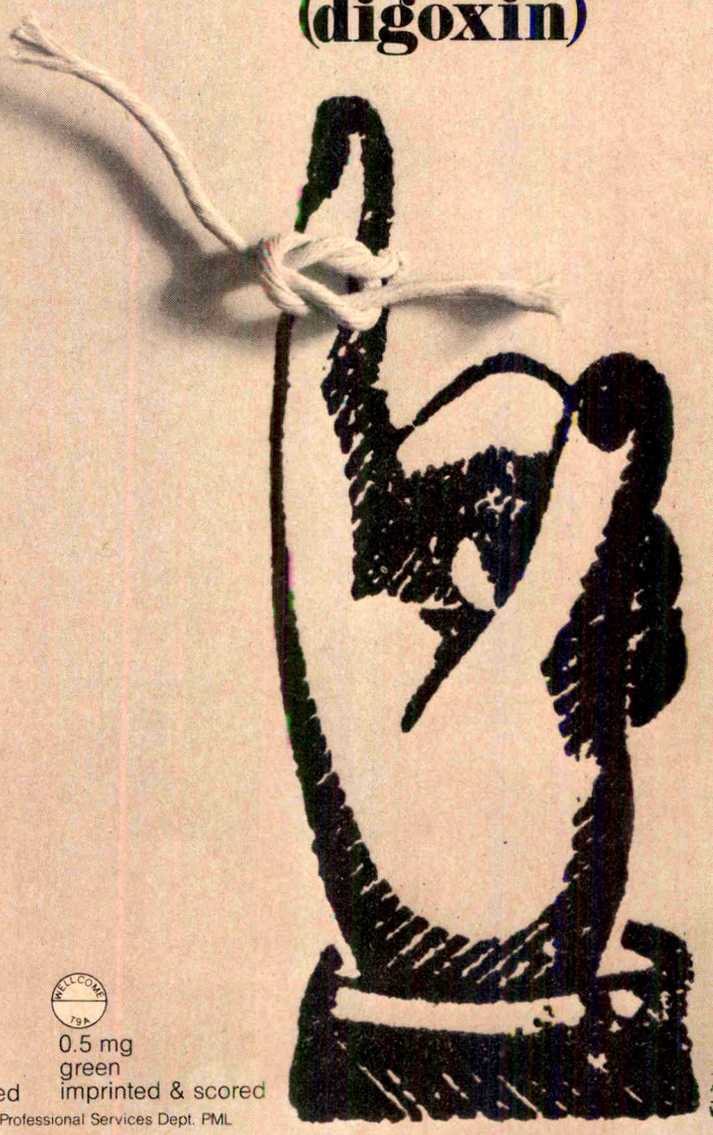
1123 Paroxysmal Supraventricular Tachycardia: An Electrophysiologic Approach

MARK E. JOSEPHSON

Modern electrophysiologic techniques permit differentiation of "paroxysmal atrial tachycardia" into several electrophysiologically distinct arrhythmias whose treatment depends on knowledge of the mechanism of the arrhythmia. As discussed in this editorial, certain clinical clues helping to elucidate these mechanisms include P wave contour, relation of the P wave to the QRS complex of the tachycardia, the presence of bundle branch block and its effect on the tachycardia, and the effect of atrioventricular dissociation on the tachycardia. It is in patients with recurrent disabling arrhythmias that electrophysiologic studies offer important data for making therapeutic decisions.



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SYMPOSIUM ON NEW ASPECTS OF ANTIARRHYTHMIC THERAPY

Douglas P. Zipes, MD, FACC, Guest Editor

Introduction: Miles To Go

DOUGLAS P. ZIPES, MD, FACC

Indianapolis, Indiana

It is of interest to reflect that, just 15 years ago, when a patient presented with an acute myocardial infarction, he was placed in a regular hospital room, occasionally one located close to the nurses' station, given an analgesic agent for pain, an anticoagulant drug and, sometimes, an oral antiarrhythmic agent. Concepts of coronary care monitoring and therapy, effective cardiopulmonary resuscitative techniques and electrical cardioversion were in their infancy. Embryonic in the early 1960's, these three concepts have matured to provide the foundation for many of the clinical advances achieved in control of cardiac rhythm disturbances in the last one and one half decades.

In this minisymposium, it was not possible to recapitulate all the recent progress made in the therapy of cardiac arrhythmias. Rather, the approach has been to obtain selected reviews from several prominent investigators who have made original, important contributions in the area of patient care and to the understanding, as well as management, of cardiac rhythm disturbances. These investigators provide a reflective review of the current state of the art in their special area of interest and expertise. Lown and DeSilva present observations linking the psyche with the heart and the role of the autonomic nervous system in preventing, permitting or precipitating the development of cardiac arrhythmias. Woosley and Shand review the present understanding of pharmacokinetic principles, necessary for correct use of antiarrhythmic agents. Harrison and associates, intimately acquainted with the role of long-term recordings of the cardiac rhythm in ambulatory patients, discuss the use of this technique in arrhythmia management. Our contribution is a review of some of the newer antiarrhythmic agents that we have used and that may become approved for clinical use in the United States sometime in the future. The last two topics, the application of pacing techniques, by Wellens et al. and the use of surgery, by Gallagher et al., represent innovative therapeutic approaches to the treatment of cardiac rhythm disturbances not responding to conventional measures.

Many topics not discussed, in which progress has been gained in understanding or treating cardiac arrhythmias, include out-of-hospital ventricular fibrillation, its cause, treatment and prevention; mechanisms of arrhythmogenesis and drug therapy in patients with tachyarrhythmias associated with the Wolff-Parkinson-White syndrome; mechanisms responsible for supraventricular and, in some instances, ventricular

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tachyarrhythmias; use of new recording techniques such as body surface mapping, signal averaging and intracardiac methodology. The entire area of basic cardiac electrophysiology, which serves as the wellspring for much of our clinical knowledge, is not considered. These topics and others could easily fill several more symposia.

As expected, in spite of the progress achieved, more questions remain unanswered than answered. We still do not fully understand the electrophysiologic mechanisms of many tachyarrhythmias in man, particularly those arising in the ventricles, and, even when we do, we are unable to predict with accuracy which drug will effectively control which specific arrhythmia. Particularly when treating ventricular tachyarrhythmias, control of each patient's rhythm disturbance remains an individual pharmacologic experiment, the results of which are learned by empiric trial and error. Arrhythmias, almost capriciously, may respond to only one of two drugs with similar actions, for example, to quinidine but not to procainamide. Anecdotes about cases in which a particular drug suppressed a ventricular tachycardia refractory to all other agents exist for virtually every antiarrhythmic drug. As an example, one of our patients recently received a trial of 10 different antiarrhythmic agents until a drug was found that successfully suppressed his life-threatening ventricular tachycardia. Multiple drug regimens often must be tried for some patients until a successful combination of drugs is found. Perhaps acute drug testing, advocated by Lown, represents an initial approach to solving this problem by providing rapid screening methods, somewhat analogous to testing the sensitivity of an organism to an antibiotic drug. Complicating this approach, however, is the fact that the tachyarrhythmia to be suppressed is not always present when therapy is being evaluated. We need reliable methods of initiating the tachycardia, such as stress testing or premature electrical stimulation of the heart, as well as reliable methods for evaluating the patient's response to therapy, such as attempts to reinitiate the tachycardia or the use of ambulatory recordings after therapy has been started. It is important to recall that the usual electrocardiogram, on which many physicians base the need for, as well as the response to, therapy represents approximately 1/1,440 of a patient's day. As pointed out by Harrison, significant variability occurs throughout the day in the frequency of many arrhythmias, and therapeutic decisions based only on the 12 lead electrocardiogram may lead to errors in judgment.

Present status of antiarrhythmic therapy: It may be as naive to think that one antiarrhythmic drug will be effective for all patients as it is to think that one antibiotic agent will cure all infections. Therefore, we need to be able to choose from a wide selection of antiarrhythmic agents that have widely different electrophysiologic properties. No ideal universally effective antiarrhythmic agent exists. If it did, such questions as whom to treat and with what drug would not occur. Virtually all of the available antiarrhythmic agents have significant side effects, and, because of this, therapy should be looked on as substituting one disease for another. One must constantly appraise whether the "disease" (antiarrhythmic agent) given to the patient carries more risk than the disease (arrhythmia) being treated. The present state of antiarrhythmic therapy basically involves administering a drug potentially toxic to the myocardium to treat an abnormal condition. Correcting the abnormal state, rather than creating another, but different one, intuitively seems more appropriate, but such an approach can be used in only selected instances. One hopes that in the future, understanding the metabolic or cell changes associated with the genesis of arrhythmias may provide insight into therapy that actually reverses basic defects rather than simply suppresses them. Until that time, however, clinicians must continue to use wisely the existing forms of therapy, constantly evaluating the benefit to risk ratio. As is the requirement when administering investigational drugs, physicians using conventional drugs should inform patients of potential side effects before initiating therapy.

It is important to realize that the pathophysiologic basis of cardiac arrhythmias may be a changing event. Particularly during the evolution of a myocardial infarction, the electrophysiologic mechanisms responsible for ventricular arrhythmias may change with time. Within minutes of occluding the coronary artery in dogs, the initial ventricular arrhythmias probably result from reentry occurring in ischemic myocardium; ventricular arrhythmias present 12 to 24 hours later may be due to abnormally enhanced automaticity, possibly arising in or near injured, but surviving Purkinje fibers; after 2 to 3 days, ventricular arrhythmias can again be elicited that may be caused by reentry excitation. Differences in the type of the infarction, transmural or subendocardial, also may create a different pathologic substrate establishing different electrophysiologic events. Therefore, it should not be surprising that the same drug may suppress arrhythmias in one patient with an acute myocardial infarction, but not in another patient, or at one time during the evolution of an infarction in one patient, and not at another time in the same patient. This point is easily documented in the laboratory. In our canine experiments, aprindine given *before* coronary occlusion, increases the spontaneous development of ventricular fibrillation, but given to dogs experiencing ventricular tachycardia 24 hours *after* coronary occlusion, aprindine is profoundly antiarrhythmic. Thus, in the dog, the same drug can be arrhythmogenic or antiarrhythmic, depending on the time it is given in relation to the coronary occlusion. It is our belief that any antiarrhythmic agent that significantly slows conduction, particularly in the acutely ischemic myocardium, which may be more sensitive to such slowing effects than is the normal myocardium, is capable of enhancing the potential for developing areas of unidirectional block conducive to reentry excitation. Conversely, drugs that improve conduction in the ischemic myocardium may be antiarrhythmic. It would appear to be an oversimplification to think that an antiarrhythmic agent with a negative dromotropic effect converts a single area with unidirectional block to one exhibiting bidirectional

block, thus preventing reentry from occurring. The myocardium is a complex three-dimensional syncytium and, particularly when ischemia results in heterogeneous effects, many islets with different functional properties probably exist. Antiarrhythmic agents cannot affect the entire area uniformly and may abolish the propensity to develop reentry in one area but create it in another. Tacit to this reasoning is the assumption that the antiarrhythmic agent actually reaches the site of origin of the arrhythmia, which may not be so if a vessel is totally occluded, without collateral vessels to the ischemic or infarcted area.

Patients already receiving an antiarrhythmic agent at the time of their infarction may represent an entirely different "model" than the patient who has already had an infarction and is then given an antiarrhythmic drug in the coronary care unit. The first clinical situation may be more similar to when an experimental animal is given a drug before coronary occlusion, and the second situation to when the drug is given after coronary occlusion.

Role of experimental models for testing drug efficacy: The adequacy of experimental models in which to test the efficacy of an antiarrhythmic approach must be considered. Information regarding the effects of various agents on the electrophysiologic properties of isolated Purkinje fibers or cardiac muscle must be obtained from "sick" as well as healthy tissue preparations. After all, most situations of antiarrhythmic therapy involve patients with "sick" hearts. The response to drugs, to autonomic nervous system manipulation or to other interventions, of arrhythmias induced in various animal models by aconitine, digitalis, catecholamines, electrolyte changes, ischemia or hypoxia provides important information. However, in the final analysis, determination of whether an approach will suppress arrhythmias in man cannot be obtained by even the most elegant in vivo or in vitro studies in animals, but must be established by critical clinical studies in man himself. This consideration in no way invalidates or even minimizes the importance of experimental animal studies, which provide insight into understanding mechanisms of arrhythmia development and of the action of antiarrhythmic agents and which often suggest new areas for future research. Communication between the laboratory and the bedside must be fluid and bidirectional. Clinicians capitalized on the observation by Moe that a supraventricular tachycardia in a dog could be started or stopped by premature stimulation. Conversely, many laboratory experiments have been conducted to confirm the elegant concepts gleaned from the surface electrocardiogram by Katz, Pick and Langendorf.

Role of clinical drug testing: Drug studies in man must be carefully designed and even more carefully interpreted; they must take into consideration the nature of the patient's illness and arrhythmia. For example, in patients with stable recurrent premature ventricular complexes, it seems relatively easy to test the efficacy of an antiarrhythmic agent by comparing data obtained during an adequate control period with similar data obtained during a treatment period. Studies can be single or double-blinded with a placebo control. Long-term drug therapy may be discontinued periodically during the patient's course to be certain that the arrhythmia has not spontaneously ceased. When comparing the efficacy of one drug with another, parallel studies in matched populations or a blinded cross-over study using a placebo control, with an adequate washout period in between drug testing, may be used. However, clinical studies of these types raise certain issues, such as the duration of an adequate control period. A single 24 hour recording interval is often used, but some data suggest it may not be sufficient. A more important question involves the meaning of the results derived from such studies. What can be concluded regarding efficacy, if the drug achieves a 75 or even 90 percent reduction in the number of premature ventricular complexes in a stable, asymtomatic population? Obviously, therapy is a failure if it has suppressed 90 percent of the premature ventricular complexes but fails to prevent a single episode of ventricular fibrillation. Because such studies are generally performed in patients who have nonlife-threatening ventricular arrhythmias that do not produce symptoms and who may not need any treatment, the results obtained may not necessarily be applicable to patients with recurrent ventricular tachycardia or ventricular fibrillation that produces syncope and presyncope. Controlled studies in this latter group are complicated by the life-threatening nature of the ventricular arrhythmia. For example, a patient who has required electrical termination of ventricular fibrillation on multiple occasions in the preceding 24 hours in spite of conventional antiarrhythmic therapy cannot be treated with a placebo to establish a control period before he receives an investigational drug. Similarly, if the ventricular arrhythmia is related to a long-term problem, and has recurred over a period of time, it is difficult to justify discontinuing what appears to be effective therapy at some future time to establish whether the propensity to ventricular fibrillation is still present. If the drug is stopped, it must be done in the hospital, while the patient is monitored. Then, if the ventricular fibrillation does not recur, how long does one wait before restarting therapy to be certain the ventricular fibrillation will not return in the future? Although it may be more difficult to apply rigorous scientific methodology to investigations in this group of patients, it is for this very group with life-threatening, recurrent ventricular tachyarrhythmias that effective antiarrhythmic therapy is needed. Whether 90 percent suppression of premature ventricular complexes alters morbidity or mortality remains to be established.

In summary, the intention of this short symposium is to review progress made in selected areas of therapy of cardiac arrhythmias and to consider some aspects in which efforts must be concentrated. New knowledge about arrhythmias occurring in patients with mitral valve prolapse or prolonged Q-T interval, or in patients with a clinically normal heart, is intriguing but it remains incomplete. We still do not know whether sup-

pression of ventricular ectopy in patients with coronary artery disease will affect sudden death, which is one of the most pressing questions to be answered in contemporary clinical cardiology. Are the premature ventricular complexes an independent marker or a precipitating force, or both? What creates the electrical instability leading to a ventricular fibrillation in patients who, after resuscitation, do not manifest a myocardial infarction, and why are these patients so prone to a recurrence? Does reperfusion of a previously occluded coronary artery, due to dislodgment of platelet thrombi or relaxation of spasm, play a role in these patients? Will premature stimulation of the ventricle expose patients prone to have life-threatening ventricular arrhythmias and sudden death? In this regard, we recently studied a patient who had been resuscitated from three episodes of ventricular fibrillation that had recurred over a 6 week period in spite of conventional drug therapy and were not associated with acute myocardial infarction. Between episodes, the patient demonstrated only occasional isolated or pairs of premature ventricular complexes, even after exercise (treadmill) stress testing. Premature stimulation of the right ventricle with single and double stimuli, delivered at the earliest moment in diastole, at several cycle lengths and at different endocardial sites failed to elicit a single spontaneous repetitive ventricular complex in this patient. Perhaps, premature left ventricular stimulation would have been more revealing. Or perhaps, if ventricular fibrillation is an "electrical accident" resulting from evanescent electrical instability, such testing may not be predictive at all, because factors causing the electrical instability are not present at the time of testing, even though the anatomic substrate is abnormal. Finally, if such a test is useful, does it measure the "overall" propensity to fibrillate or only that triggered by an R on T event?

It is clear that we have made great strides in recent years, but much remains to be done:

The woods are lovely, dark and deep
But I have promises to keep
And miles to go before I sleep
And miles to go before I sleep.

—Robert Frost
*Stopping by Woods on a Snowy Evening**

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Roles of Psychologic Stress and Autonomic Nervous System Changes in Provocation of Ventricular Premature Complexes

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Neural and psychologic factors have been implicated as risk factors for ventricular arrhythmias and sudden death in man. However, the relation between these factors and arrhythmia has hitherto not been systematically explored. We examined the effect of psychologic stress testing in 19 patients with advanced grades of ventricular arrhythmias. Psychologic stress consisted of mental arithmetic, reading from colored cards and recounting emotionally charged experiences. Such testing induced a significant increase in ventricular premature beat frequency in 11 of 19 patients ($P < 0.05$). One patient experienced paroxysms of ventricular tachycardia. In 14 of these 19 patients elicitation of vagal or sympathetic autonomic reflexes failed to induce significant arrhythmia in all but one patient. It is concluded that (1) objective psychologic tests may precipitate ventricular arrhythmia in susceptible patients, and (2) evocation of peripheral autonomic reflexes is an insufficient trigger for enhanced ventricular ectopic activity.

The clinician is often confronted with events suggesting a relation between psychologic stress and the precipitation of angina pectoris, congestive heart failure and derangements in heart rhythm. It has also been promulgated that higher nervous activity is implicated in sudden cardiac death.[1,2] A substantial literature[3] provides convincing evidence that in animal models the autonomic nervous system plays a role in the genesis of diverse cardiac arrhythmias. However, objective studies in man linking psychologic stresses to the occurrence of arrhythmias are noteworthy for their paucity. The very complexity of the psychologic dimension, the subjective quagmire one is rapidly entrapped in when attempting to define stress and the multiplicity of interacting cybernetic loops when dealing with higher nervous activity are but a few of the factors contributing to the poverty of investigative efforts.

Cortical and subcortical inputs to the heart have been deemed transient risk factors for sudden cardiac death.[1,2] The basis for such speculation relates to the fact that neither a consistent anatomic nor a hemodynamic precipitating basis for ventricular fibrillation has been identified. When patients are resuscitated from cardiac arrest, normal electrical activity is restored and ensuing life expectancy is determined by the extent of myocardial disease. Sudden cardiac death is thus a reversible electrophysiologic derangement rather than the inexorable culmination of far advanced coronary arterial atherosclerosis incompatible with survival. Among the possible transient factors that momentarily alter cardiac excitability and account for this reversible electrical accident, one must consider the continuously modulating effect of neural activity upon cardiac electrophysiologic properties. A subsidiary question relates to the relative roles of peripheral autonomic reflex changes and central psychophysiologic variables in the genesis of ventricular arrhythmias.

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TABLE I

Underlying Heart Disease and Type of Ventricular Arrhythmia In 19 Patients Subjected to Psychologic Stress Testing

Case no.	Sex	Heart Disease	Highest Grade of Arrhythmia Documented	
			At Any Time	During Hospitalization
1	M	CHD (MI)†	VF	4B
2	F	CHD (MI)*†	VF	4B
3	M	CHD (MI)†	VF‡	4B
4	M	CHD*†	VF‡	4B
5	M	CHD	VF‡	VF
6	M	CHD†	VF	0
7	M	CHD (AP)	4B	4B
8	M	CHD (MI)†	4B	4B
9	M	CHD (MI)	4B	4B
10	M	CHD (MI)	4B	4B
11	M	CHD (MI)	4A	4A
12	M	CHD (MI)	3	2
13	M	Normal†	3	2
14	F	Normal†	VF‡	4B
15	M	Normal†	4A	4A
16	M	Normal†	4B	4B
17	M	Cardiomyopathy†	VF‡	4B
18	M	IHSS†	4B	4B
19	M	Mitral valve prolapse	4B	4B

* After coronary bypass operation.
† Cardiac catheterization and coronary angiography.
‡ Recurrent ventricular fibrillation.
AP = angina pectoris; CHD = coronary heart disease; IHSS = idiopathic hypertrophic subaortic stenosis; MI = myocardial infarction.

TABLE II

Grading of Ventricular Premature Beats

Grade	
0	None
1A	Occasional, isolated (<30/hr)
1B	Infrequent, >1/min (<30/hr)
2	Frequent (>30/hr)
3	Multiform
4A	Repetitive, couplets
4B	Ventricular tachycardia
5	Early (R on T)

In this report we present preliminary data examining the role of psychologic stress as well as the effects of sympathetic and vagal cardiovascular reflexes in provoking ventricular arrhythmia. The patient population studied had high grades of ventricular ectopic activity or had been resuscitated from sudden cardiac death. This study was part of an effort to ascertain if ambient psychologic stresses were a factor in the genesis of the patient's arrhythmia so that management could be focused in this direction.

Materials and Methods

Patient population: Nineteen patients were studied, 17 male and 2 female, whose ages ranged from 18 to 67 years. Table I presents the type of heart disease and arrhythmia exhibited by this group. Twelve had coronary heart disease as determined from a history of angina pectoris, previous documented myocardial infarction or by coronary arteriography. Two patients were subjected to coronary artery bypass operation, but this procedure failed to control recurrent ventricular fibrillation. In four patients who underwent cardiac catheterization and angiographic studies no significant hemodynamic myocardial or coronary artery abnormalities were detected.

Ventricular premature beats were graded as shown in Table II.[4,5]

Eight of these patients had experienced ventricular fibrillation, and in five this arrhythmia recurred frequently. Seven patients exhibited paroxysms of ventricular tachycardia that ranged from episodic brief salvos of three consecutive ectopic beats to sustained arrhythmia associated with significant hemodynamic compromise requiring cardioversion. In two patients the maximal grade was recurring ventricular couplets, whereas in the two remaining patients, frequent multiform ventricular premature beats was the highest grade achieved during ambulatory monitoring. Before the psychologic stress studies, ambulatory monitoring for 24 hours showed 4B ventricular arrhythmia to have been the maximal grade in 13 of these 19 patients. One patient, who had experienced ventricular fibrillation and had in the past exhibited frequent grade 4B arrhythmias, was entirely free of ectopic activity (Table I).

Psychologic stress test protocol: The test, consisting of three parts, was administered by a cardiologist. Oral as well as written informed consent was obtained from all patients. The initial component was mental arithmetic for 5 minutes. The patient was under time pressure to perform straightforward mathematical computation. He was alerted in a censorious manner when the calculation was wrong. The second component, also of 5 minutes' duration, consisted of reading from Stroop color cards. These cards contain the names of four colors (blue, green, red and yellow). The letter type of each color is different from the name of that color. For example, the color red may be printed in blue. The patient is first asked to read the name of each color from a card printed in black and white. This task is ordinarily easy. The patient is then given the Stroop card and asked to describe the actual color of the letters in which the color name is printed. This is more difficult because the message contained in the word itself tends to interfere with the verbalization of the color. The final component of the test, lasting for 10 minutes, consisted of an interview relating to emotionally meaningful aspects of the patient's life, including the patient's illness, job-related stress, marriage and death. Such a conversation has been described to be stress-inducing.[6,7] During the entire stress testing period, lasting about 20 minutes, the patient's heart rhythm was monitored by a trendscriber[8] with the signal telemetered from a bipolar chest lead. The number of ventricular premature beats during the stress test was divided by the duration of the test to provide an average ectopic beat frequency.

The control period for psychologic stress testing was obtained from a 24 hour monitoring session either immediately before or after these studies, but not including the testing period itself. Tapes were read on an American Optical Dynagram scanner at 60 times real time, coupled to a semiautomated processing unit designed to quantify ventricular premature beats on an hourly basis as well as to provide an hourly printout of an entire hour selected at random to determine quality control.[5,9] Because the sleep period has been demonstrated to decrease the frequency as well as the grade of ventricular premature complexes,[10] it was excluded from calculations of the prevalence of arrhythmia during the control period. The mean frequency of ventricular premature complexes during the waking period was computed by dividing the total number of ectopic beats by the duration of the waking period obtained from the patient's diary. The re-

TABLE III

Frequency of Ventricular Premature Complexes (per min) in 19 Patients as a Result of Psychologic Stress Testing

Case no.	Ventricular Premature Complexes (per min)		
	Control	Psychologic Stress	Difference
1	6.8	36.5	+29.7
2	19.2	16.3	−2.85
3	1.8	0	−1.80
4	0.32	0.91	+0.50
5	0.92	5.92	+5.00
6	0.02	0	−0.02
7	0.68	0.91	+0.23
8	2.68	2.32	−0.54
9	1.71	2.0	+0.29
10	0.97	2.43	+1.46
11	4.65	6.23	+1.58
12	0.11	0	−0.11
13	0.08	0	−0.08
14	15.2	27.05	+11.85
15	0.06	0	−0.06
16	0.07	0.76	+0.69
17	0.62	0.13	−0.49
18	0.04	12.35	+12.31
19	0.29	11.88	+11.59
Mean	2.96	6.62*	+3.66

* $P < 0.05$.

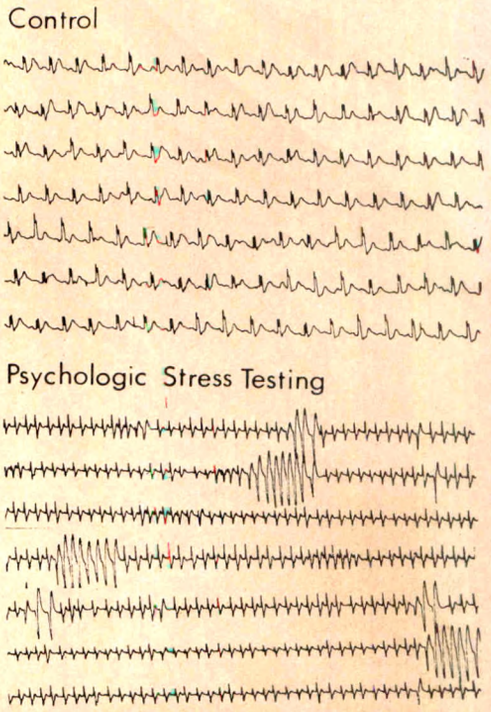


FIGURE 1. Ventricular tachycardia induced by psychologic stress testing (monitor leads). **Top,** control tracing preceding test shows sinus rhythm at 65 beats/min. (During the preceding 24 hours of monitoring, no advanced grades were recorded.) **Bottom,** during psychologic stress testing, heart rate increased to 92 beats/min, and recurrent runs of supraventricular tachycardia and ventricular tachycardia occurred.

quency was expressed as ventricular premature complexes per minute of awake time. The mean heart rate was likewise obtained for the waking period. Statistical comparisons were made between frequency of ventricular premature complexes and heart rate during the control and test period.

Autonomic reflex testing: Cardiovascular reflexes were studied in 14 of the 19 patients who underwent psychologic stress testing. The study was conducted in a quiet, softly lit room; conversation was kept to a minimum. A full explanation was given before the test, and frequent reassurance was employed throughout the procedure to avoid provoking psychologic stress that may accompany these maneuvers. No invasive instrumentation was used. The patient assumed a supine position on a tilt table and lay quietly for at least 10 minutes before control measurements were made.

The patient was told beforehand of each maneuver to be performed. A 1 minute control 12 lead electrocardiogram was recorded and the test was conducted during monitoring of standard lead II. Electrocardiographic strips were recorded for 10 seconds before and after each maneuver, as well as during the maneuver itself.

The following maneuvers were carried out in sequence, allowing adequate time for recovery between maneuvers:

1. Head-up tilt to 70 degrees.
2. Breath-holding for 30 seconds (upright).
3. Hyperventilation for 30 seconds (upright).
4. Return to supine position for at least 5 min to allow resumption of control heart rate.
5. Right carotid sinus massage.
6. Left carotid sinus massage.
7. Valsalva's maneuver for 30 sec.
8. Elicitation of the "dive reflex" by means of cold application to the face.

The "dive reflex" was evoked in a nonapneic manner by using a plastic bag filled with ice and water. The bag was placed to cover as much of the face as possible, but without interfering with breathing. This avoided the added effects of breath-holding or Valsalva's maneuver. Heart rate was determined during the maximal change with each procedure. Measurements were made just before and after completion of the Valsalva maneuver. The grade and frequency of ventricular arrhythmia were scored during or after each procedure and compared with the control electrocardiogram.

Results

Psychologic Stress Testing

Arrhythmic frequency: In 11 patients, the frequency of ventricular premature complexes was increased during stress; of these, 7 had a twofold or greater increase in arrhythmia. In 8 patients, ventricular ectopic frequency during the test was less than that during the control period. The mean frequency of ventricular premature complexes for the entire 19 patients in the control period was 2.96/min compared with 6.62/min during the psychologic stress period. Wilcoxon signed rank testing showed that this increase for the entire group during the stress period was statistically significant ($P < 0.05$) (Table III). Of the seven patients with recurrent 4B arrhythmia, six showed a mean increase of 4.42 ventricular premature complexes/min, whereas only one showed a decrease during psychologic stress testing and this was by a modest 0.54/min. Of the eight patients with ventricular fibrillation, four showed an increase and four a decrease in ventricular premature complex frequency. However, the mean increase for the four patients was 11 ventricular premature complexes/min of the testing period, while in those showing a de-

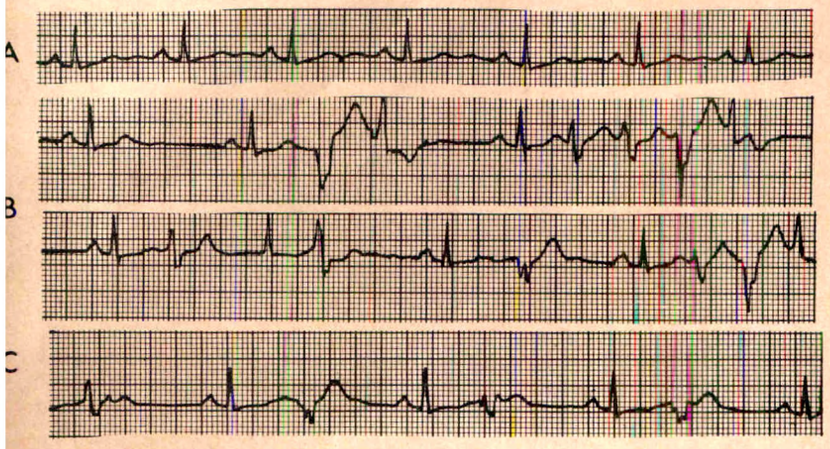


FIGURE 2. A, control tracing (lead II) before application of cold stimulus to the face; sinus rate is 72 beats/min. **B,** continuous strips; 30 seconds after facial exposure to cold, sinus bradycardia and repetitive multifocal ventricular premature beats are evoked. Sinus rate is 47 beats/min. **C,** ventricular bigeminy persists 5 minutes after cessation of the cold stimulus, even after the sinus rate had returned to a normal range. Sinus rate is 82 beats/min.

crease, it did not exceed 1 ventricular premature complex/min. Of the 12 patients with coronary heart disease, 7 showed enhanced ventricular ectopic activity, and five showed no change or a slight reduction.

Severity of arrhythmia: Assessment of repetitive grade 4 activity was difficult because these forms were sporadic and rare; however, of the 11 patients who exhibited this grade during 24 hour monitoring, 7 demonstrated either couplets or paroxysms of ventricular tachycardia during the much briefer period of psychologic stress, which was only 1/48 the duration of the control period. The enhancement of advanced grades of arrhythmia was strikingly illustrated in one patient (Case 5) with a history of recurrent episodes of ventricular tachycardia and fibrillation. Although he was free of complex forms of arrhythmia during the control monitoring period of 24 hours as well as during mathematical and Stroop card testing, when the discussion was focused on his retirement and current illness he began to experience malignant paroxysms of ventricular tachycardia (Fig. 1). These abated when the conversation was redirected and the patient reassured.

Analysis of heart rates in these 19 patients showed mean increases from 71 ± 2 beats/min during the control period compared with 82 ± 4 beats/min during psychologic stress ($P < 0.01$). The relation between changes in heart rate and changes in ventricular premature complex frequency was examined in all 19 subjects by computing Kendall's tau statistic. The value of tau was 0.23, which indicates a significant concordance ($P < 0.01$) between increases in heart rate and increases in ventricular premature complex frequency during psychologic stress testing in this group of patients.

Autonomic Reflex Testing

Fourteen patients in the study group underwent testing of cardiovascular autonomic reflexes. In 10 of the 14 patients, no arrhythmia was noted during the control period. In these patients activation of vagal or sympathetic reflexes did not elicit ventricular premature complexes. The comparison time was 1 minute of monitoring that preceded the test procedures. In three patients infrequent and sporadic ventricular ectopic complexes were noted throughout the test procedure, unrelated to any specific provocative vagal or sympathetic maneuver. The grade of ventricular ectopic activity was unaffected in these three patients. Significant arrhythmia was provoked in only one patient. This patient (Case 14) was a highly neurotic woman; results of cardiac catheterization and coronary arteriography were entirely normal. Despite continuing reassurance, she was brimming with anxiety and apprehension. Bigeminy occurred with tilting and during Valsalva's maneuver. Hyperventilation completely abolished the arrhythmia. During elicitation of the dive reflex she exhibited two couplets and one three beat run of ven-

TABLE IV

Heart Rate Response to Autonomic Reflex Maneuvers of 10 Normal Subjects and 14 Patients With Ventricular Arrhythmias

Study Group	Control	Tilt	Post-Tilt	Breath-Holding	Hyperventilation	RCSP	LCSP	Valsalva	Post-Valsalva	Dive Reflex
Normal subjects (no. = 10)	64 ± 3*	69 ± 5	78 ± 5	75 ± 4	106 ± 7	57 ± 4	55 ± 3	73 ± 4	66 ± 6	57 ± 4
Patients (no. = 14)	69 ± 3	79 ± 4	82 ± 3	82 ± 3	96 ± 6	53 ± 4	58 ± 3	82 ± 6	80 ± 4	68 ± 2
P value	NS	NS	NS	NS	NS	NS	NS	NS	<0.05	<0.02

* Values are expressed as mean ± standard error of the mean. LCSP and RCSP = left and right carotid sinus pressure, respectively; NS = not significant; *P* = probability.

tricular tachycardia; at this point her heart rate had slowed to 48 beats/min (Fig. 2).

Comparison of these 14 patients with 10 normal control subjects in relation to heart rate changes during autonomic reflex testing is shown in Table IV and Figure 3. Comparison of mean heart rates between normal subjects and patients was performed using Student's *t* test for unpaired data. Heart rates were normalized by dividing the heart rate during each procedure by the control heart rate obtained before autonomic reflex testing and expressed as a fraction of the control heart rate to permit comparison of the two groups. There was no significant difference in heart rate response between the two groups except during the post-Valsalva period (phase IV) and during activation of the dive reflex. The patient group showed significantly less reduction in heart rate than the control group during these two periods.

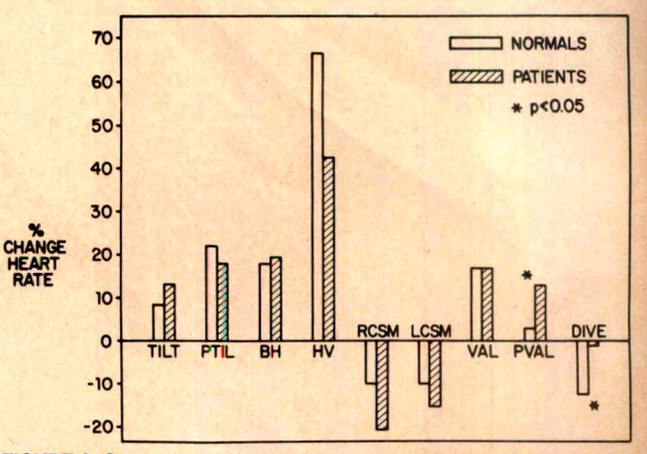


FIGURE 3. Comparison of heart rate response to autonomic maneuvers in 14 patients with ventricular arrhythmia and 10 normal subjects. Heart rates are expressed as percent of control heart rate to permit comparison between the two groups. BH = breath-holding; DIVE = dive reflex; HV = hyperventilation; LCSM = left carotid sinus massage; p = probability; PTIL = 2 minutes after tilting; PVAL = post-Valsalva maneuver; RCSM = right carotid sinus massage; TILT = 30° head-up tilt; VAL = Valsalva maneuver.

Discussion

Previous experimental arrhythmias: In animal models psychologic stresses of diverse types have been associated with the occurrence of arrhythmias. Newton et al.[11] reported nonsustained atrioventricular block in pointer dogs bred for nervousness when these animals were subjected to Pavlovian conditioning. Such a response was not obtained in normal animals. In a very small group of dogs maintained on an atherogenic diet for over 4 months, prolonged restraint in a Pavlovian sling for 9 hours daily was accompanied by delivery of brief random electric shocks.[12] Two of four animals with a high cholesterol level manifested ventricular premature beats terminating in ventricular fibrillation. Arrhythmia was not observed in control groups.

In another series of experiments, dogs were exposed to two different environments: a cage in which the animal was left undisturbed, and a Pavlovian sling in which the animal received a single 5 joule transthoracic shock at the end of each experimental period for 3 successive days.[13] The effects of the two environments on the animals were compared on days 4 and 5. On these days, dogs in the sling became restless, frequently salivated excessively, exhibited somatic tremor and had a mean heart rate of 136 beats/min. The repetitive extrasystole threshold during cardiac pacing at a constant rate was used as a measure of vulnerability to ventricular fibrillation. In the cage environment, the current that elicited repetitive extrasystoles was 43 ± 5 milliamperes (± standard error of the mean); in the sling environment the mean threshold was significantly reduced to 14 ± 6. The animals with the highest nonpaced heart rates in the sling also had the greatest reduction in threshold for repetitive extrasystoles. The type of psychologic stress was not critical; thus, when dogs were trained instrumentally to avoid electric shock, this aversive setting also reduced the repetitive extrasystole threshold by 50 percent.[14] Various psychologic stresses have also been shown to provoke major ventricular arrhythmias in conscious animals in the absence or presence of myocardial ischemia.[7,15–17]

Previous clinical observations: Whereas in animals convincing evidence is being marshalled indicating the potentiality of diverse psychologic stresses to disorganize heart rhythm and even induce ventricular fibrillation, no such decisive data exist in man. The role of psychologic stress in provoking ventricular arrhythmia has wide interest and clinical currency.[7,18–23] The expressions "frightened to death" and "scared to death" are common to most human languages and such examples are chronicled in folk and medical lore.[18] An early report described paroxysmal ventricular tachycardia precipitated in a young neurotic woman by emotional stress.[20] Taggart and others[21,22] systematically explored cardiac responses to diverse stresses induced by car racing, driving in traffic and public speaking as well as to thermal, physical or emotional stresses. Multiple ventricular ectopic beats emerged in 5 of 24 patients with ischemic heart disease while they were driving their own car along a familiar route.[21] Thirteen of these patients also showed significant ischemic S-T segment and T wave alterations. Public speaking exposed more than 6 ventricular extrasystoles/min in 6 of 23 normal subjects, and prolific ectopic activity in 5 of 7 patients with coronary artery disease. A single oral dose of 40 mg of the beta adrenergic blocking drug oxprenolol suppressed these abnormalities.[22] In a remarkable case, Wellens et al.[23] reported the consistent precipitation of syncope when the patient, a 14 year old girl, was awakened from sleep by auditory stimuli. An alarm clock or any other sound that roused her was accompanied by rate acceleration, Q-T prolongation, T wave inversion, emergence of early ventricular premature beats and ventricular fibrillation. This sequence was reproducible.

Psychologic factors as precipitants of sudden death: In the absence of Q-T interval prolongation a relation between psychologic factors and sudden death

has at best been demonstrated only circumstantially. Ward rounds conducted by the chief of service have been shown to trigger sudden death among patients convalescing from acute myocardial infarction.[24] A recent case study[25] perhaps provides the most direct evidence for a probable relation between psychologic variables and the occurrence of ventricular fibrillation. The patient, a 39 year old man, twice experienced ventricular fibrillation and had frequent ventricular premature complexes. He had normal coronary arteries and no indications of structural heart disease. Evidence adduced for higher nervous activity in the genesis of the ventricular arrhythmia included the psychiatric makeup of the patient, the emotional stress attending the first cardiac arrest, the provocation of advanced grades of ventricular premature beats and ventricular tachycardia by psychiatric visits, the prevalence of arrhythmia during the rapid eye movement (REM) stage of sleep when the patient had violent dreams, the occurrence of the second episode of ventricular fibrillation during a similar period of sleep and the fact that digitalis and a cardioselective beta adrenergic blocking drug decreased ventricular ectopic activity.

Ventricular arrhythmia and psychologic stress: Is the precipitation of ventricular arrhythmia in man mediated by peripheral autonomic reflex changes, or are these only inadequate triggers requiring additional inputs to the heart from higher nervous centers? This study was structured to examine the relation between induced psychologic stress and peripheral neural reflex alterations and the frequency of ventricular premature beats. This study was conducted under controlled clinical conditions. Because of the uncertain outcome in the use of psychologic stress, our initial approach was a cautious one. Patients were only mildly stressed using nonspecific stressors such as mental computations and an attempt to provoke uneasiness. The nature of the conversation had a content that would have been elicited by a physician in the course of obtaining a careful history. That this approach was indeed mildly stressful is indicated by the modest increase in heart rate. These psychologically stressful maneuvers increased the frequency of ventricular premature beats. In order to make certain that these do not represent merely random changes in ventricular ectopic frequency, a long control period was utilized for comparison. This prolonged period no doubt included intervals of stress, which necessarily are an integral part of the hospital milieu. Patients were not shielded from the ordinary stresses and diverse intrusions and indignities that necessarily accompany hospital life. Why some patients did not respond with an increase in ventricular arrhythmia and even had a decrease is not clear. The latter we believe represents sporadic variability rather than an actual diminution. In no patient was it greater than 3 ventricular premature complexes/min and, barring one patient, the mean decrease was less than 0.5/min. Conversely, the increase in ventricular premature complex frequency, also excluding the single patient with the largest alteration, was by 4 complexes/min.

It is self-evident that psychologic stress is highly individual. Whether an event is stressful depends on a complex amalgam of factors including genetic predisposition, early growth and developmental experience, a lifelong process of conditioning, as well as an array of cultural factors that constitute the psychologic prism through which daily events are uniquely and individually refracted. It is well known that what may seem stressful to one may even be pleasurable to another. It is therefore surprising that the generalized and relatively mild stressors utilized in our study enhanced the frequency of ventricular ectopic activity, and in one patient resulted in malignant ventricular tachycardia.

Ventricular arrhythmias and peripheral autonomic reflexes: It is of interest that in this same study group peripheral autonomic neural manipulations attending tilting, Valsalva's maneuver, carotid sinus massage, breath-holding, hyperventilation and activation of the dive reflex did not affect the frequency of ventricular arrhythmia. Wolf[26] suggested that the dive reflex may be a factor in sudden death, and Wayne and Killip[27] showed that this maneuver may stimulate cardiac arrhythmias. Scholander et al.[28] studied native Australian pearl divers and demonstrated significant reductions in heart rate, the occurrence of ventricular premature complexes, idioventricular rhythm, inversion of T waves and atrial fibrillation. Breath-holding and hyperventilation[29] were also reported to produce ventricular arrhythmias. In this present preliminary and ongoing investigation we examined both sympathetic and parasympathetic cardiovascular reflexes in patients with high grades of ventricular arrhythmias. There was a striking lack of arrhythmia during these autonomic maneuvers. Only one patient had significant enhancement of ventricular premature complexes during the test. This patient was a highly emotional, easily distraught and hysterical woman with no myocardial, heart valve or coronary artery disease. She had had recurrent episodes of cardiac arrest brought on by emotional conflicts with her husband and other family members. During the test she was nervous and anxious, whereas none of the other patients displayed anxiety because constant reassurance was employed. Thus, the tests represented the passive evocation of autonomic responses with but a minimum of adverse psychologic content. The different results we obtained in comparison with those of other workers[26–29] may in part be explained by the special care taken in our study to avoid the effects of emotional stress during these autonomic maneuvers. The integrity of autonomic nervous system reflexes was examined by comparing heart rate responses during the maneuvers in patients and control subjects. There were no substantial differences in heart rate change except during the post-Valsalva phase and facial exposure to cold. The latter observations suggest there may have been impairment in vagal response in the patient group.

Implications: One may surmise that "passive" alteration in peripheral autonomic neural tone is not

sufficient to precipitate ventricular arrhythmias, barring far advanced heart disease. Input from higher nervous centers may thus be a necessary element in providing the type of neural traffic that disorganizes cardiac rhythm. Our preliminary findings demonstrate that induced psychologic stress can enhance ventricular arrhythmia. The mechanisms for this remain to be defined; however, enhanced sympathetic nervous activity is undoubtedly implicated. Although the peripheral autonomic system acts as part of the response pathway for cerebrocortical initiated activity, it may not exert a decisive role in the absence of such higher neural input. A further implication of these findings is that in the management of patients with recurrent life-threatening arrhythmias, the physician will have to be attentive to the psychophysiologic variables that may play a role in the genesis of this disorder.

Acknowledgment

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Pharmacokinetics of Antiarrhythmic Drugs

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A knowledge of the determinants of the plasma concentrations of antiarrhythmic drugs is important because variation in plasma levels is often greater than the desired therapeutic range. The basic principles of pharmacokinetics are outlined and their application to the design of dosage regimens described. These principles are illustrated in a review of the pharmacokinetics of lidocaine and its congeners, procainamide and its active metabolite (N-acetylprocainamide), quinidine, disopyramide, phenytoin and propranolol, with particular emphasis on the factors that contribute to altered disposition.

Nowhere in medicine is the value of a working knowledge of pharmacokinetics better illustrated than in the management of antiarrhythmic drug therapy. Not only are the effects of these drugs (both bad and good) predictably related to their plasma concentration, but also this class of drugs in general has a relatively narrow therapeutic ratio; that is, the toxic concentration only exceeds the effective level by two- or threefold. In addition, the plasma concentration after a given dose may vary quite widely from patient to patient, so that it requires considerable skill to adjust the dosage regimen so that effective levels are achieved without exceeding those associated with toxic or adverse reactions. In this review we first describe the basic principles of simple pharmacokinetics and then show how they can be applied to the management of patients with use of the more commonly used antiarrhythmic drugs. At the outset, it should be stressed that kinetics can only be used as a guide to initial therapy; thereafter, drug dosage should be adjusted according to the clinical outcome.

Pharmacokinetics

Basic Principles

Once a drug has been absorbed or injected into the body, two basic processes, elimination and distribution, determine its concentration at any given time. Drug elimination is assessed from the measurement of clearance, which is defined as the volume of plasma or blood cleared of drug in unit time. Because clearance has units of flow, it can be related to organ blood flow to give a measure of the efficiency of elimination. For example, if a drug is cleared at a rate of 750 ml/min by the liver, which has a blood flow of 1,500 ml/min, then 50 percent of the drug delivered to the liver is removed in a single pass, so that the extraction ratio is 0.5.

The concentration of a drug (C_{ss}) that has been infused until a steady state is reached depends only on drug clearance (Cl) and the infusion rate (I), as follows:

$$C_{ss} = \frac{I}{Cl}$$

After the administration of multiple intermittent intravenous doses has led to a steady state, drug clearance and dose (D) also determine the average concentration (C_{av}) achieved and the area under the plasma concentration/time curve

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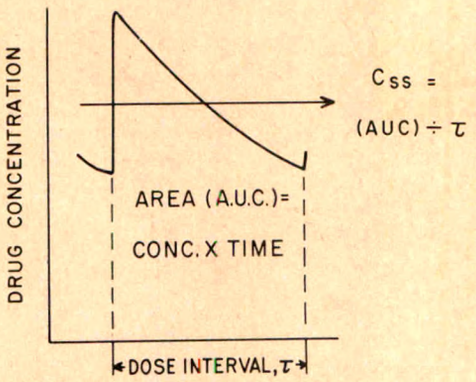


FIGURE 1. Steady state concentrations (C_{ss}) and area under the concentration/time profile (A.U.C.) depend only on dose and drug clearance. CONC. = concentration; t = time.

(AUC) during the dosage interval (Fig. 1), so that

$$AUC = \frac{D}{Cl}$$

and

$$C_{av} = \frac{D}{Cl \times \tau}$$

in which τ is the time interval between doses. It can be seen that C_{av} is the same as C_{ss} obtained by constant infusion of D units of drug every τ minutes. Changes in volume of distribution *do not* affect steady-state drug levels, although this commonly is thought to be the case. Obviously, however, drug concentrations do increase and decrease when drugs are given intermittently, and in this situation volume of distribution can affect the drug concentration present at any particular time after administration.

The volume of distribution of a drug is determined by the relative degree of binding or uptake by the tissues compared with that in blood or plasma where drug is sampled. It is defined as the volume of blood (or plasma) into which the mass of drug in the body (M) must be diluted to result in a given plasma concentration (C), so that

$$Vd = \frac{M}{C}$$

The concentration of drug at any given time, C_t, is therefore determined both by volume of distribution and by the mass of drug present, which in turn is determined by the dose and the amount eliminated over the time since the drug was first administered. For most drugs elimination proceeds as a first order process; that is, the rate of elimination is proportional at all times to drug concentration. Under these circumstances drug clearance represents a constant fraction (k) of the volume of distribution (Vd) so

$$k = \frac{Cl}{Vd}$$

In fact, k is the first order rate constant for elimination and has units of time^{-1}. This can be converted to the more common expression, drug half-life ($T_{1/2}$) as

$$k = \frac{0.693}{T_{1/2}}$$

so that

$$T_{1/2} = \frac{Vd \times 0.693}{Cl}$$

This is perhaps the most important of pharmacokinetic equations and assumes that the body is a single homogeneous compartment. It also illustrates the fact that drug half-life depends on both volume of distribution and drug clearance.

To summarize, if a drug is injected rapidly (and we do not generally recommend this) its initial concentration (C_0) is determined by volume of distribution (Vd) and dose (D) according to the equation $C_0 = D/Vd$ because little drug has been eliminated in the short time taken to inject it. Thereafter, drug removal is proportional to concentration, which decreases exponentially because the reduction of drug concentration results in a progressive reduction in the amount of drug eliminated in any given time period (Fig. 2). This curve can be converted to a straight line plotting drug concentration as a logarithmic function against time, or as in the case of Figure 2 (right), using semilog paper. Drug half-life is, by definition, the time taken for drug levels to fall to one half of their initial value, so that after 1 half-life 50 percent of the drug is left in the body. After another drug half-life, levels will fall by a further 50 to 25 percent and 75 percent of the dose will have been eliminated. The amount of drug left in the body after various half-lives are shown in Table I, and it can be seen that after 5 half-lives most of the drug is eliminated.

Drug Accumulation

It takes a finite time after starting a given dose of a drug for plasma concentrations to reach their eventual steady-state level. In addition to describing the rate of reduction of drug concentration, the drug half-life also

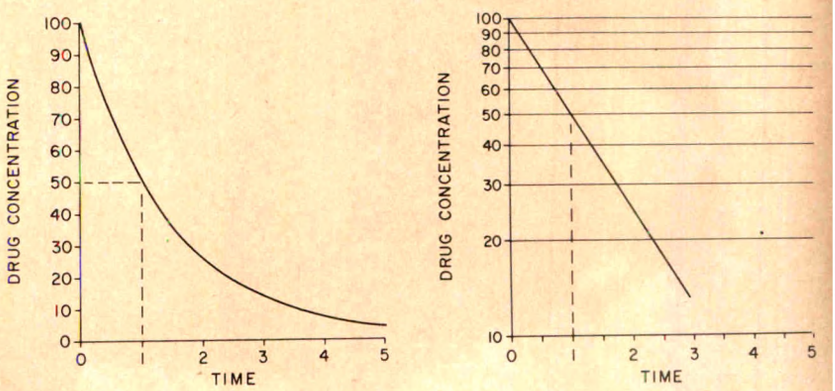


FIGURE 2. Drug concentration with time during first order elimination for a single compartment plotted on an arithmetic scale **(left)** and on a semilog scale **(right).**

TABLE I

Effects of Half-Life on Drug Elimination and Accumulation

Half-Lives (no.)	% Remaining*	% Accumulation†
1	50	50
2	25	75
3	12.5	87.5
4	6.25	93.75
5	3.125	96.875

* The fraction of the amount in the body or initial plasma level present various times after a single dose.

† The fraction of the final steady state drug concentration achieved at various times during continuous drug administration.

describes the rate of accumulation to steady state during a constant infusion. In fact, the time course of accumulation is the mirror image of that for elimination, for the following reason: Steady state is defined as that situation in which the rate of removal is equal to the rate of delivery of drug so that plasma concentrations remain constant. One half-life after beginning drug administration 50 percent of the drug will have been eliminated and 50 percent retained. But both drug concentration and the rate of removal will have increased so that, during the second half-life, 75 percent of the drug will have been eliminated and a further 25 percent will have been retained. This process continues until the rate of removal increases to equal the rate of delivery. The percent of the final steady-state levels achieved after various half-lives of infusion are also given in Table I, which shows that more than 90 percent of the steady-state level is reached after 3 or 4 half-lives. It should be emphasized that doubling the rate of infusion will not alter the time taken to obtain the steady state but will double the drug concentrations achieved.

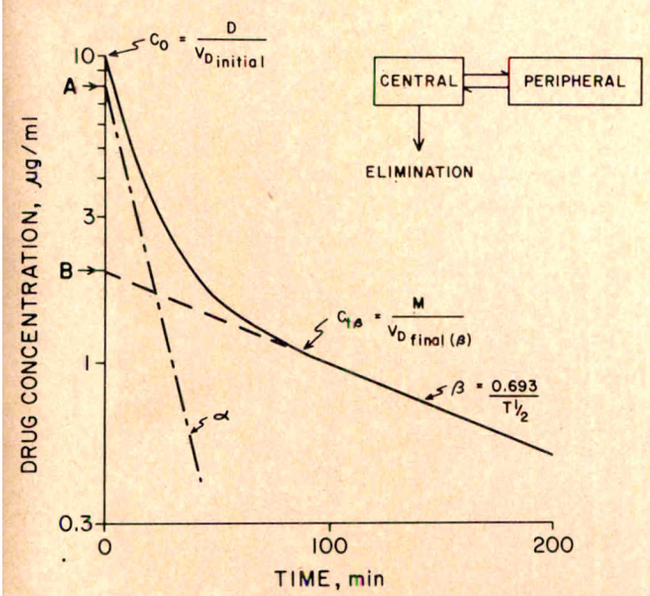


FIGURE 3. Drug concentrations after intravenous administration show a biphasic curve (that is, two-compartment system). $C_{t\beta}$ = final drug concentration; C_0 = initial drug concentration; D = dose; M = mass of drug in the body; T1/2 = half-life; $V_{Dinitial}$ = initial volume of distribution; $V_{Dfinal(b)}$ = final volume of distribution.

Loading and Maintenance

Single intravenous loading dose: Because the time taken to reach a steady state may be too long in patients requiring urgent treatment, the use of loading and maintenance doses are often required, as in the case of the cardiac glycosides. There are several ways to achieve the desired effect relatively rapidly. The first involves the use of a single loading dose. In the case of the antiarrhythmic drugs given intravenously, this is not satisfactory because the peak levels attained are usually associated with adverse effects. This occurs because the concentration/time profile of these drugs after intravenous administration is, in fact, biexponential, an early rapid phase of reduction being followed by a slower decrease in concentration. In this situation the body acts as if it were composed of two compartments, a central one that reflects plasma concentrations and from which elimination occurs, and a peripheral one, that comprises those tissues that equilibrate slowly with plasma (Fig. 3). As a result, immediately after injection drug concentration (C_o) is determined by the dose (D) and the volume of the central compartment or the initial volume of distribution (Vd) (C_o = D/Vd). Because drug distributes out of this compartment into the tissues at the same time as it is eliminated, the measured volume of distribution increases from its initial value and drug

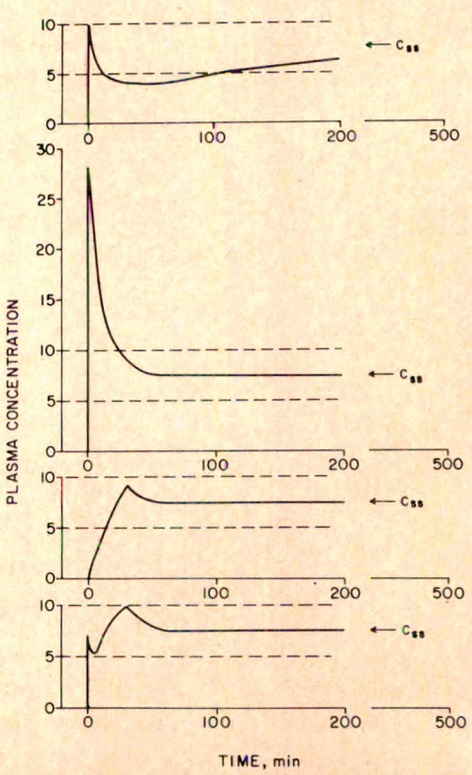


FIGURE 4. Alternatives for loading and maintenance regimens after intravenous administration. C_{ss} = drug concentration when a steady state is achieved.

concentrations fall rapidly to reach a value determined by the mass of drug in the body and the volume of distribution at the time the late phase of elimination becomes a single exponential. This is the final volume of distribution (Vdβ).

Loading dose followed by maintenance infusion: If we try to give such a drug as a single dose followed by an infusion designed to give steady-state levels in the middle of the therapeutic range, two equally undesirable effects may be seen (Fig. 4). When the single dose is adjusted to avoid peak levels in the toxic range, plasma levels "dip" below therapeutic levels for a time before the concentrations due to the infusion rise into the therapeutic range. This occurs because the rate of rise of concentrations due to the infusion is determined largely by the terminal or β-phase half-life. In the example used (Fig 4, top panel) the half-life is 100 minutes so that levels due to the infusion would have risen to only 30 percent of steady state by 50 minutes, at which time levels after the injection would have fallen to 30 percent of their initial value of 10 μg/ml. The resultant sum of these two therefore falls below minimal effective levels. The second alternative of giving a large enough single dose to ensure therapeutic levels throughout is just as unsatisfactory because toxic levels may be attained for an appreciable time (Fig. 4, second panel). Put another way, the difference between peak and equilibrium levels (which is dependent on the ratio of initial and final volumes of distribution) often exceeds the therapeutic ratio.

Double infusion technique: To avoid these problems, a double infusion technique, whereby a rapid infusion is followed by the maintenance infusion, has been advocated.[1] Although this type of regimen is available for all of the antiarrhythmic drugs, safety is achieved at the expense of the time taken to reach the therapeutic range (Fig. 4, third panel). While the double infusion technique is often satisfactory, urgent treatment can be initiated and maintained by giving a single injection followed by the double infusion (Fig. 4, bottom panel). However, it should be stressed that the single dose or rapid infusion rate, or both, should be reduced because plasma concentrations will be the sum of the two.

Oral Administration

After oral administration the distribution phase is generally obscured by the absorptive phase and can be ignored for practical purposes. The factors influencing drug elimination and volume of distribution are the same as those previously described, but in addition we must consider the fraction of the dose that reaches the systemic circulation and then the target organ—that is, systemic availability. Availability may be reduced by (1) incomplete absorption, and (2) metabolism by the intestine or liver, during the passage of drug from the gut lumen to the systemic circulation. This latter effect is called presystemic or "first pass" elimination and it occurs with several antiarrhythmic drugs.

Because the body generally behaves as a single compartment after oral drug administration, only drug clearance and the terminal half-life need be considered in designing dosage regimens. Recognizing the narrow therapeutic ratio of the antiarrhythmic agents, it is the usual practice to give such drugs every half-life or so, because then peak and trough levels should not differ by more than a factor of two. The dose is then adjusted so that trough levels are above the minimal therapeutic concentration. Consequently, the optimal time for obtaining plasma concentrations for monitoring purposes is at the end of the dosage interval.

Factors Influencing Drug Disposition

Several factors are known to alter the clearance and distribution of antiarrhythmic compounds in both health and disease. The biological determinants of drug disposition are (1) the activity of the basic removal process (intrinsic clearance), (2) organ blood flow, and (3) drug binding in the blood and tissues. All of these may be influenced by constitutional and environmental factors in apparently healthy people, as well as by heart failure, renal failure and liver disease. Consequently, it is the rule that plasma concentrations vary widely (up to 10- to 20-fold) when the same dose is given to a group of people. However, the effects of all of these factors can be judged on the basis of the known pathophysiology of disease and the mechanism reponsible for the disposition of any given drug. With this information, dosage regimens can be simply designed to fit the needs of any given patient, at least as a first approximation.

Lidocaine and Its Congeners

Clearance related to hepatic blood flow: Lidocaine is eliminated by metabolism in the liver, which is extremely efficient in removing the drug from the circulation. As a result of this high hepatic extraction ratio, the clearance of lidocaine approaches hepatic blood flow. Furthermore, because the liver can eliminate almost all of the drug delivered to it, lidocaine clearance is greatly influenced by alterations in liver blood flow.[2] The therapeutic range of plasma lidocaine levels in 1.6 to 5.0 μg/ml. In patients with relatively normal hepatic blood flow and function, plasma clearance is about 10 ml/kg per min. As shown earlier, the infusion rate at steady-state level is equal to plasma concentration times clearance (3 μg/ml times 10 ml/kg per min). Thus, to achieve steady-state levels of 3 μg/ml, an infusion rate of 30 μg/kg per min will be required. In patients with heart failure, clearance is reduced to about 60 percent of normal, probably as the result of reduced liver blood flow that accompanies an increase in cardiac output. Thus an average maintenance dose of 18 μg/kg per min should be instituted in such patients. A similar reduction in dosage is needed in patients with obvious liver disease, because they also have reduced clearance due to altered hepatic function and a decrease in blood flow.

Loading dose regimens: Several loading dose regimens have been suggested. As mentioned previously, a single loading dose is unsatisfactory for lidocaine because the volume of distribution at equilibrium exceeds

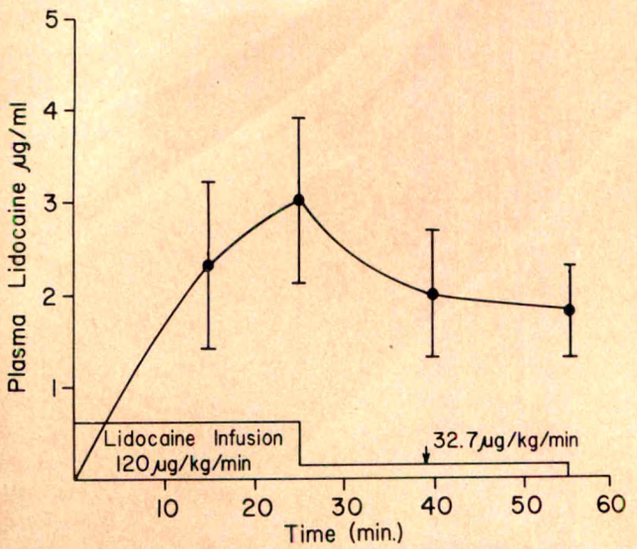


FIGURE 5. Double infusion technique for lidocaine. **Bars** represent standard deviation (no. of patients = 13).

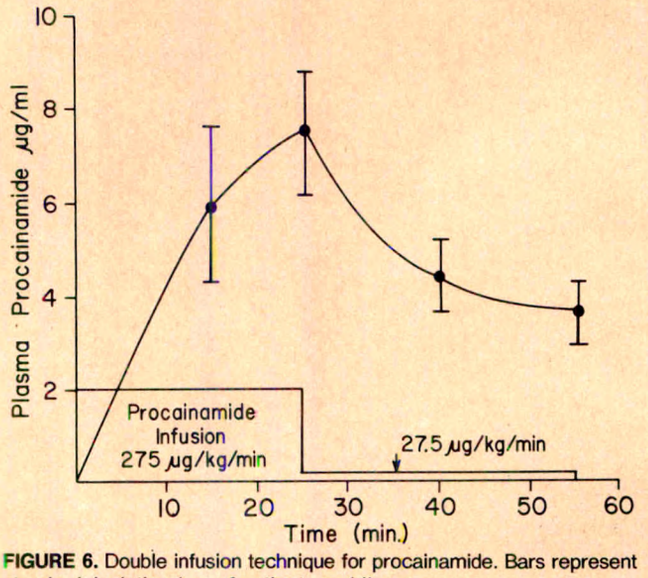


FIGURE 6. Double infusion technique for procainamide. Bars represent standard deviation (no. of patients = 14).

the initial volume of distribution by a factor of about 3, which is greater than the ratio of toxic to therapeutic plasma concentrations. To overcome this disadvantage a series of small loading doses has been suggested by Benowitz et al.[3] based on the fact that the half-life of the distribution phase is about 8 minutes. A total loading dose of 3.9 mg/kg is given as four injections at 8 minute intervals, the first (1.5 mg/kg) being about double the subsequent three injections of 0.8 mg/kg. Another approach has been to give a more rapid infusion for a relatively short time and follow it with a lesser maintenance infusion.[1] We have illustrated this from our own experience of giving patients with stable arrhythmias a rapid infusion of 120 µg/kg per min over 25 minutes and then a maintenance level of 32.7 µg/kg per min (Fig. 5). Clearly, the rates of both of these infusions should be reduced to 60 percent in heart failure. In liver disease, the initial volume of distribution is little changed so the initial loading injections need not be altered. However, because of the reduced clearance, maintenance infusion rates should be reduced to about 60 percent. Finally, Aps et al.[4] have recently suggested that a suitable regimen would be a single injection (over 2 minutes) of 50 to 100 mg followed by an infusion of 4 mg/min for 30 minutes, 2 mg/min for 2 hours and then 1 mg/min. This regimen was clearly better than a single loading dose and maintenance infusion because it avoided the "dip" in concentrations to below therapeutic levels that occurs 1 to 3 hours after loading. In patients requiring urgent therapy a similar approach would be to give a 50 mg dose, then a more rapid infusion and, finally, maintenance infusion.

Figure 4 illustrates another important point: Even when an apparently accurate and rational regimen is used, considerable individual variation will still occur. Thus, the rate of the maintenance infusion must be adjusted every 1 to 2 hours according to the patient's response.

Accumulation of metabolites: In patients receiving prolonged lidocaine infusions after myocardial infarction, it was observed[5,6] that lidocaine levels continued to rise for about 48 hours and that the half-life, which is usually about 100 minutes after single doses or shorter infusions, was prolonged to up to 4 hours. The precise reason for this unexpected accumulation is unclear, but the finding suggests a progressive reduction in clearance with prolonged infusions. In this context there was also an increase in two metabolites of lidocaine that have some pharmacologic activity. The monoethylglycine xylidide metabolite (MEGX) possesses some antiarrhythmic effect[7] and the glycine xylidide metabolite (GX) potentiates the convulsant action of lidocaine and MEGX.[8] Until the mechanism of this accumulation and the precise role of active metabolites has been resolved, any potential hazard can be minimized by titrating dose to antiarrhythmic effect without side effects on the central nervous system.

Potential factors that might influence lidocaine disposition: Such factors other than liver disease and heart failure have not been thoroughly investigated although it has been shown that renal disease is without effect. In particular, certain drug interactions have not been investigated in man, but animal studies have shown that propranolol,[9] which decreases cardiac output and hepatic blood flow, and norepinephrine,[10] which reduces hepatic blood flow, decrease lidocaine clearance and increase plasma levels. Other animal studies have shown that lidocaine clearance is increased by phenobarbital,[11] presumably by microsomal enzyme induction, and by isoproterenol[10] or glucagon,[12] which increase hepatic blood flow.

In addition to the pharmacokinetic interactions, the use of lidocaine in the presence of other drugs could potentially cause pharmacodynamic interaction. In particular, we would be concerned about the use of large single doses of lidocaine in patients receiving propran-

olol. Although it is yet unreported, we suspect that the cardiac depression that can occur soon after a bolus injection of lidocaine[13–15] might be potentiated by the abolition of compensatory sympathetic reflexes in the presence of beta blockade.

Lidocaine Congeners

Oral administration of lidocaine is not generally recommended because the high hepatic extraction ratio results in significant presystemic elimination of some 80 percent of the dose. When four or five times greater doses are used to attain therapeutic levels of lidocaine, the four- to fivefold increase in the active metabolites achieved results in considerable side effects. Consequently, an attempt has been made to develop congeners that are less efficiently extracted by the liver. Both tocainide and mexilitene have achieved this aim and are effective orally.[16–18] Neither agent is yet available clinically, but they show promise for the future because of their systemic availability when administered orally and their relatively long half-life of about 10 hours.

Procainamide and N-acetylprocainamide

Procainamide: The pharmacokinetics of procainamide are somewhat complicated because this drug is eliminated about equally by hepatic and renal routes. Acetylation is one route of metabolism and this is affected by acetylator phenotype in that both rapid and slow acetylators exist. Finally, the acetylated metabolite N-acetylprocainamide (NAPA, acecainide) has antiarrhythmic activity. Many of the complexities are beginning to be resolved and several therapeutic regimens have been introduced in the past 5 years. The first attempt to rationalize procainamide therapy was made by Koch-Weser.[19] Because the half-life of the drug was known to be about 3 hours in patients with normal renal and hepatic function and the therapeutic window 4 to 8 μg/ml, it was suggested that a loading dose of 1 g should be followed by half this dose every half-life (that is, every 3 hours). In many patients with heart disease these doses should be reduced by 25 percent. Subsequently, Giardina et al.[20] devised a regimen for intravenous therapy that involved giving 100 mg doses at 5 minute intervals, until either a therapeutic effect was achieved, 1 g had been given or toxic effects appeared. The effect could usually be maintained with an infusion rate of 2 to 4 mg/min. We recently applied the double infusion technique (Fig. 6) based on the fact that the average clearance of the drug is about 500 ml/min in patients with normal renal and hepatic function.[21]

Procainamide is quite well absorbed by mouth (75 to 95 percent), but plasma levels show very wide variability (up to 10-fold) when the same dose is given to a group of patients. This makes the use of an average dose an approximation at best. Thus, although average concentrations of 6 μg/ml are achieved by giving about 50 mg/kg (that is, 3.5 g) daily, in many patients the concentration falls above or below the desired therapeutic range, necessitating individual titration of the dose. If large doses are needed, or toxicity is suspected, then plasma level determinations can be most helpful. As mentioned, a 3-hourly dosing interval is needed to keep peak and trough levels of procainamide from varying more than twofold. However, this type of regimen is exceedingly difficult for most patients to comply with, and 4 to 6 hourly dosing is often the best that one can hope to achieve.

N-acetylprocainamide: The recent discovery of the antiarrhythmic efficacy of N-acetylprocainamide may necessitate adjustment of these regimens under certain circumstances. This metabolite of procainamide has recently been shown to have antiarrhythmic actions of its own and is under development as a drug in its own right.[22,23] In contrast to the parent compound it is almost entirely (85 percent) eliminated by the kidneys with a lower clearance of the order of 180 ml/min. The half-life in patients with normal renal function is about twice that of procainamide (that is, 6 to 8 hours). Although extensive information is not yet available, the effective range of concentrations is 2 to 22 μg/ml (mean 11 μg/ml in seven patients) and levels as high as 40 μg/ml appear to be well tolerated.[23] The possible involvement of N-acetylprocainamide may explain the clinical experience that the dosage interval for procainamide may sometimes be increased to about 6 hours, in contrast to the 3-hourly regimen recommended by Koch-Weser.[19]

Role of cardiac and renal failure in kinetics: In patients with heart failure procainamide is cleared less well, and a reduction in dosage by 30 to 50 percent in initial therapy is recommended for patients with severely compromised cardiac function. The effects of renal failure have a relatively predictable effect on procainamide kinetics. The total clearance of the drug is reduced because of a reduction in that fraction eliminated by the kidneys in proportion to the decrease in creatinine clearance. For example, a 50 percent reduction in creatinine clearance would reduce the renal clearance of the drug from the normal value of 250 to 125 ml/min. The clearance by metabolism should remain at 250 ml/min, so that overall clearance would be 75 percent of normal, giving about 30 percent higher levels. However, in addition, the clearance of N-acetylprocainamide, which is 85 percent dependent on renal function, would be expected to fall with creatinine clearance, and its levels rise more dramatically. Indeed Drayer et al.[24] have recently demonstrated very high N-acetylprocainamide levels that persisted with a very prolonged half-life in patients with severe renal compromise. Clearly the use of procainamide in such patients, if it cannot be avoided, is best achieved with careful monitoring of both procainamide and N-acetylprocainamide levels as well as a clinical assessment of efficacy and toxicity.

Quinidine

Improved analytical capabilities in recent years have made it possible to study quinidine metabolism, and several metabolites have been identified. One of these has been found to have antiarrhythmic activity[25] and may contribute to the total therapeutic effects. One problem that has evolved from improved analytical

techniques is that the therapeutic window for quinidine was established using the nonspecific assay[26] that measured active drug, active metabolites and inactive metabolites. The newer double extraction method measures only active drug, and a new therapeutic window for this assay must be established. Kessler et al.[27] determined the therapeutic range for 14 patients using the double extraction method and found it to be 2.3 to 5 μg/ml, a considerably lower range than that obtained with older methods.

Kinetics of intravenous infusion: Ueda et al.,[28] in a recent study using a specific assay method, established the kinetics of quinidine gluconate after an intravenous infusion of 250 mg over 22 minutes in patients with normal renal and hepatic function. They confirmed that the drug is eliminated almost entirely by metabolism, only 17 percent of the dose being excreted unchanged in the urine. Plasma clearance averaged 4.7 ml/kg per min with a large range of 1.5 to 7.1 ml/kg per min. They confirmed the usually reported half-life of 6.3 hours (range 3.6 to 8.2). The generally low clearance of the drug in relation to liver blood flow demonstrates the poor hepatic extraction and explains the good bioavailability (76 percent) of the drug. It also suggests that the kinetics of the drug in normal people would not be materially affected by route of administration.[29] The intravenous route has not generally been recommended in therapy, largely because of the circulatory depression likely from single large doses. However, this slower infusion has been found safe in patients studied to date.[30] Clearly further information on the causes of the large interindividual variation in plasma levels attained by a given dose[31] will be needed before this approach is generally applied.

Kinetics of oral preparations: Quinidine is most commonly given by mouth and several preparations are available. Greenblatt et al.[32] recently compared the kinetics of the sulfate and the gluconate salts in normal volunteers. Quinidine sulphate was rapidly absorbed, with peak levels at about 1.5 hours. About 80 percent (61 to 100 percent) of the dose was available to the systemic circulation. In contrast, the gluconate was more slowly absorbed with peak levels at 4 hours after dosing. This salt was less available than the sulfate (71 percent). More importantly, systemic availability was more varied with the gluconate (40 to 93 percent). In comparing the preparations, it would be expected that the gluconate could be given less frequently (every 8 to 12 hours) than the sulfate (every 6 to 8 hours) because of its more prolonged absorption phase, which also results in lower peak levels.

This principle of prolonging absorption (without changing elimination half-life) in order to increase duration of action is used in the commercially available slow-release preparations of both sulfate and gluconate salts. A polygalacturonate salt is available and has similar properties. In prescribing these various preparations it should be remembered that they contain different amounts of the quinidine base. The sulfate contains 83 percent of the base, the gluconate 62 percent and the polygalacturonate 60 percent. These differences have to some extent been accounted for in formulation, as a 324 mg tablet of the gluconate (Dura-tabs®) is equivalent to 240 mg of quinidine sulfate, and a 275 mg tablet of the polygalacturonate (Cardioquin®) equivalent to 200 mg of quinidine sulfate.

Dosage: The actual dosage required in any given patient can vary quite widely as a result of individual variation, the effects of disease, other drugs and formulation differences. An initial total daily dose of 600 to 900 mg is generally recommended, the actual dose and dosage interval depending on the preparation. If needed, the dose should be gradually increased in increments of about 50 percent with careful electrocardiographic monitoring for signs of early toxicity (prolonged QRS and Q-T intervals). Quinidine is potentially so toxic and its kinetics so variable that plasma level monitoring is highly desirable. Concentrations of 1.5 to 3 μg/ml at the end of the dosage interval are generally considered therapeutic; levels of 7 μg/ml or greater are associated with a large incidence of toxicity.

Effects of renal, hepatic or cardiac failure: The effects of disease on quinidine kinetics have been investigated by Kessler et al.,[27] who compared the two analytical methods in patients with renal or hepatic failure and determined that nonactive fluorescent metabolites accumulate at levels of active drug that are not excessive. They concluded that quinidine dosage should not be reduced in patients with renal failure, a recommendation consistent with the minor role played by the kidneys in elimination.

The effects of congestive heart failure upon quinidine kinetics has been examined after oral and intramuscular administration. Analysis of these data by Crouthamel[33] indicated that congestive heart failure leads to reduction of the rate of absorption and the volume of distribution of the drug, with little change in half-life. These effects would tend to give somewhat higher peak plasma levels that develop at later times in patients with heart failure, although the differences are relatively small compared to known individual variation.

Data et al.[34] recently reported an important drug interaction that can potentially reduce the efficacy of quinidine therapy. They found after treatment with phenobarbital or phenytoin an increased elimination of quinidine that returned toward control level 2 weeks after discontinuation of the inducer. Induction of metabolism can change a previously effective dosage to an ineffective dosage, as was described in their index case.

Disopyramide

Disopyramide is a newly introduced antiarrhythmic agent with an effective range of plasma concentrations of 2 to 4 μg/ml.[35] It is fully absorbed and eliminated by the kidneys with a terminal half-life of 5 to 6 hours in normal persons.[36] The kinetics of this drug were recently investigated in patients with myocardial infarction and were predictably shown to be somewhat different from those of young healthy people. Ward and Kinghorn[37] reported that postinfarction patients achieved about twofold lower concentrations of disopyramide after the oral administration of 100 mg than normal subjects, who attained peak levels of about 3

μg/ml. The reason for this is not clear, but the fact that patients have 50 percent lower clearance levels and a somewhat reduced volume of distribution after intravenous administration of this drug[38] suggests that absorption is less than complete in patients with myocardial infarction. Rangno et al.[38] also showed that in such patients the drug had a somewhat reduced clearance and prolonged half-life of about 12 hours, presumably as a result of reduced renal function. On the basis of their data, these workers suggest that a suitable intravenous regimen would be 2 mg/kg over 15 minutes, then 2 mg/kg over the next 45 minutes, followed by a maintenance infusion of 0.4 mg/kg per hour. With an average clearance level of 57 ml/min, plasma levels should be about 4 μg/ml. Clearly, these doses should be reduced further in patients with greater reductions in creatinine clearance.

Phenytoin

Metabolism and dosage regimens: Phenytoin (diphenylhydantoin) is eliminated entirely by metabolism, and its therapeutic range is 10 to 20 μg/ml. It is an excellent example of a drug whose metabolism becomes saturated over the therapeutic range of concentrations. Under these circumstances drug clearance becomes progressively reduced and half-life is prolonged as the dose increases. Furthermore, the dose at which metabolism becomes saturated varies quite widely from patient to patient,[39] so that average pharmacokinetic values can only be an approximation at best and the maintenance dose must be increased more slowly than usual. In practice, the use of plasma level monitoring with this drug is almost mandatory. An approximate half-life of 22 hours may be used as a guide. As a result, 3 or 4 days will be required to reach a steady state, and a loading regimen is needed for rapid therapy. In general, 750 to 1,000 mg in divided doses is required for loading and should be followed by administration of 300 to 400 mg daily. With the intravenous route, small (50 to 100 mg) injections should be given slowly (to avoid arrhythmias or hypotension), each over 5 to 10 minutes until toxicity results, as manifested by the development of nystagmus, or 1,000 mg has been given.[40] When the oral route is used, an initial dose of 300 mg can be followed by 200 mg doses every 2 to 3 hours, up to the point of toxicity or a total of 900 to 1,100 mg.

Effects of other drugs and disease states: Because phenytoin metabolism can be influenced by a variety of other drugs, with co-administration phenytoin levels may be either increased or decreased (Table II). In general, these pharmacokinetic interactions should be monitored with plasma level measurements whenever another drug is introduced to the regimen.

The binding of phenytoin to plasma proteins (principally albumin) can be altered in disease states and has both dynamic and kinetic effects. Because the effects of a drug are generally related to its free (unbound) concentration, the decreased binding that has been noted in renal failure,[42] hypoalbuminemia[43] and the nephrotic syndrome,[44] will tend to increase efficacy. However, drug clearance will also be enhanced as more free drug is available for metabolism by hepatic enzymes, resulting in lower total plasma levels and a shorter half-life.[44] This effect is counterbalanced by an increase in the proportion of the drug in the free (active) form. The major importance of these changes is that for a given dose the same free drug concentration is associated with lower total plasma levels, which therefore cannot be used for accurate monitoring. In this situation, it may be necessary to measure the free drug if arrhythmia control is difficult. Reduced phenytoin binding has also been reported with sulfisoxazole, phenylbutazone, salicylic acid and hyperbilirubinemia in vitro,[41] suggesting that the ratio between total and free drug may also be disturbed under these circumstances.

TABLE II

Drug Interactions with Phenytoin

Inhibitors of Phenytoin Metabolism	
Bishydroxycoumarin	Prochlorperazine
Chloramphenicol	Chlordiazepoxide
Isoniazid	Diazepam
Chlorpromazine	
Stimulators of Phenytoin Metabolism	
Carbamazepine	Phenobarbital

Propranolol

The therapeutic range of propranolol concentrations in the treatment of arrhythmias is not yet clearly defined. Coltart et al.[45] showed that plasma levels of 40 to 80 ng/ml were effective in 8 of 12 patients with ventricular ectopic beats. These levels are in the range of those producing considerable cardiac beta adrenergic blockade.[46] Recently, however, Woosley et al.[47] reported that some patients may require higher levels (up to 1,000 ng/ml) to abolish ventricular arrhythmias. This therapeutic effect occurs at the expense of only mild side effects (usually fatigue) and, in occasional patients, increasing dosage to give levels above 100 ng/ml may cause recurrence in a previously well controlled arrhythmia. These findings suggest a mechanism other than simple beta blockade.

Kinetics of intravenous administration: Propranolol is eliminated entirely by hepatic metabolism, and its kinetics illustrate the effects of very efficient hepatic removal. Thus after intravenous administration propranolol clearance (1.0 liters/min) approaches liver blood flow, so that its elimination is flow-dependent as with lidocaine. Thus, individual variation in plasma levels by this route largely reflect hepatic blood flow differences, which are approximately two- to threefold.[48] Systemic clearance also decreases with advancing age (unpublished observations) probably as the result of diminished blood flow attending the known decrease in cardiac output. Loading and maintenance regimens have been proposed for the intravenous administration of propranolol, but we believe it advisable to give a 1 mg test dose over 2 to 10 minutes because of the propensity for propranolol to precipitate heart failure in susceptible patients. McAllister[49] proposed a single dose followed by an infusion, and he tested kinetic predictions for

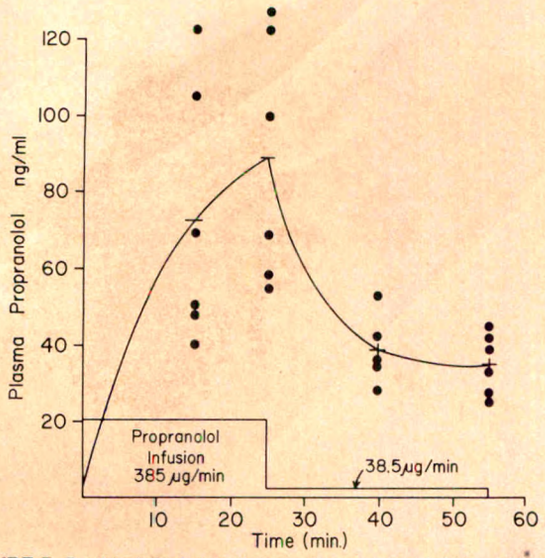


FIGURE 7. Double infusion technique for propranolol (no. of patients = 6).

three stepwise increments in dose. For example, 11.4 mg (at a rate of 2 mg/min) followed by 0.055 mg/min attained steady-state levels of 38 ng/ml after 30 minutes. A similar regimen (10 mg at 1 mg/min followed by 0.05 mg/min) gave levels of about 40 ng/ml in the study of McDevitt et al.[50] and in our experience using similar infusion rates (Fig. 7). Higher levels can be achieved by giving proportionally larger doses. After discontinuation of the infusion drug levels should decline with a half-life of 2 to 3 hours.

Kinetics of oral administration: The kinetics of propranolol are quite different after oral administration. Bioavailability of single oral doses is low because of presystemic elimination resulting from the high hepatic extraction ratio. In addition, bioavailability increases and the drug accumulates during the attainment of a steady state after continued administration,[51] so that the extraction ratio falls somewhat to about 65 percent. During the steady state, average concentrations (or AUC) depend only on intrinsic clearance (that is, the activity of the hepatic enzymes) and are not influenced by blood flow.[52] This occurs because altering blood flow produces opposite changes in extraction ratio and bioavailability. For example, reducing blood flow will increase extraction ratio so that the amount of drug entering the circulation is reduced. At the same time, clearance from the systemic circulation is reduced to the same extent, thus offsetting the changes in bioavailability.

There is a very wide variation in plasma levels (up to 20-fold) in patients given the same oral dose of propranolol. This variability is due to environmental changes superimposed on inherent individual differences. For example, levels in the elderly are about twice those in young adults. Smoking also seems to reduce levels, but largely in younger people. Finally, other drugs may well induce or inhibit metabolism. Although none have been described in clinical practice, pharmacokinetic interactions involving stimulation of metabolism (by, say, phenobarbital) is to be expected. We have also found that chlorpromazine inhibits propranolol metabolism (unpublished observations). As a result of all of these factors, average concentrations of about 50 ng/ml can be expected with 160 mg daily,[53] but the scatter in the values is so wide that this is at best an approximation. This, together with the recent suggestion that levels higher than 100 ng/ml may occasionally be required to control ventricular arrhythmias,[47] requires individual titration of the dose. Failure of therapy should not be considered until doses of 640 mg daily have been tried or side effects become limiting. Finally, we have found that some patients having experienced a satisfactory response at moderate doses (levels of approximately 100 ng/ml) show a recrudescence of their arrhythmia with increased concentration. Clearly, the full story of the mechanism of action of beta blocking agents and the therapeutic window of plasma concentrations has still to be written.

Conclusions

The most important facet of the kinetics of the antiarrhythmic drugs is that the variation in plasma levels achieved with any given dosage regimen is often much more than the therapeutic range of desirable concentrations. Although some of this variation can be predicted on the basis of known disease, such as heart failure, renal damage or diminished hepatic function, considerable differences still exist in apparently normal people. For this reason, "average" doses can only be used as an approximation and should be reduced in patients with renal or hepatic failure, dependent on the major route of elimination of the drug. A 30 to 50 percent reduction in dosage is wise in patients with obvious heart failure. Thereafter, the dose should be titrated to produce the desired effect without evidence of toxicity or development of side effects. Plasma level monitoring can be invaluable in management when a patient fails to respond or when toxicity appears to develop with moderate drug doses. Finally, pharmacokinetic factors are by no means the only factors involved in producing unexpected drug reactions in this group of patients. The ability of other drugs and electrolyte changes, particularly in serum potassium, to alter the effects of antiarrhythmic agents requires that these factors also be considered in establishing optimal therapy.

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Contribution of Ambulatory Electrocardiographic Monitoring to Antiarrhythmic Management

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To date, ambulatory electrocardiographic monitoring has contributed to our understanding of the occurrence and significance of arrhythmias. Our appreciation of the spontaneous variability of ventricular arrhythmias, the relations between symptoms and the occurrence of arrhythmias, and the use of ambulatory monitoring in documenting drug effect for new antiarrhythmic drugs and for defining relations among drug dose, plasma concentration and antiarrhythmic effect have contributed to our ability to make more rational recommendations for prescribing and monitoring drug therapy.

Further work is necessary to define the occurrence of arrhythmias in normal persons and to determine the prognostic importance of arrhythmias in normal subjects and patients with heart disease other than coronary artery disease. Studies assessing the role of spontaneous variation have indicated the problems that can occur in attempting to evaluate antiarrhythmic drug therapy in individual patients. These variations are so great that it may not be practical to monitor antiarrhythmic drug therapy in certain patients.

For patients with coronary artery disease, ambulatory electrocardiographic monitoring can identify those with frequent complex arrhythmias who are at high risk of subsequent sudden cardiac death. Such monitoring can document the effectiveness of antiarrhythmic drug therapy for ventricular irritability and define the dosing regimens or plasma concentrations that are effective for most patients. Ultimately, multicenter intervention trials must document whether or not such antiarrhythmic drug therapy can influence the outcome in the high risk patients identified with ambulatory electrocardiographic recordings. It will be important to determine whether any observed reduction in sudden death in these trials can be related to suppression of asymptomatic ventricular ectopy as determined with ambulatory electrocardiographic recordings.

Cardiologists have long appreciated the importance of precisely defining cardiac arrhythmias before administering drug therapy. However, only in recent times has it been possible to obtain objective data concerning arrhythmias in ambulatory patients. Advances in technology now permit the recording and analysis of arrhythmias occurring in cardiac patients during the course of their daily activity. These techniques permit the physician not only to detect the arrhythmias, but also to quantitate their frequency and complexity, to determine the relation of these arrhythmias to symptoms that may be present, and to determine whether or not antiarrhythmic drug therapy alters the pattern of the arrhythmia. In this paper we describe briefly the ambulatory arrhythmia monitoring systems that are available, and summarize data that are pertinent to the interpretation of arrhythmias recorded in ambulatory electrocardiograms. Finally, we will discuss the use of ambulatory electrocardiographic monitoring for evaluation of antiarrhythmic therapy.

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Importance of Ambulatory Arrhythmia Detection Systems

Before the development of ambulatory arrhythmia recording and analysis systems, physicians were dependent on patients' reports of symptoms due to arrhythmias or on the occasional recording of an arrhythmia during a routine electrocardiogram. It was virtually impossible to determine the presence of asymptomatic arrhythmias, to quantitate their frequency, to determine their spontaneous variability or to assess the immediate or long-term effects of antiarrhythmic agents. The availability of monitoring and analysis techniques now permits such study of arrhythmias both in patient populations and in individual patients. It is now possible to define the occurrence of arrhythmias in normal persons and to assess the value of determining the frequency and complexity of ventricular arrhythmias in patients with known coronary artery disease for predicting which patients are at high risk of subsequent sudden death. The widespread use of ambulatory electrocardiographic monitoring is raising many questions with regard to the occurrence of cardiac arrhythmias, to the definition of normal and abnormal cardiac rhythm and to the evaluation of drug therapy. In some instances the availability of objective data challenges old concepts on these matters. However, just as ambulatory monitoring has raised many questions, the continued widespread use of this technique in large patient populations with long-term follow-up should provide the data necessary for answering many of these questions.

Systems for Ambulatory Electrocardiographic Recording and Analysis

Recording systems: Several ambulatory electrocardiographic recording systems are available. These systems consist of small electrocardiographic amplifiers and precision amplitude modulation and frequency modulation tape recorders, capable of recording 24 or more hours of signals from electrodes attached to the patient's chest. Systems are available that use either cassette or reel to reel magnetic recording tape. Many new recording systems permit the recording of two channels of electrocardiographic data. Additionally, they have event markers or other methods of precisely correlating the time of patient symptoms with arrhythmias present on the ambulatory recording. Some recording systems provide continuous recording, whereas others record signals only intermittently. When purchasing a recording system, it is important to choose one that meets the clinical needs of the physicians who will be using it, and to be certain that the speed consistency and the frequency characteristics of the system are adequate for performing high quality electrocardiographic recordings.

Analysis systems: Both semi-automated and computer-based analysis systems for the tape-recorded electrocardiogram have been developed during the past few years. These techniques all utilize the concept of high speed playback and display of recorded data, with the ability of sampling desired portions of the electrocardiogram at real-time rates. Most analysis systems extract and display some descriptive features of the electrocardiographic data such as R-R interval, QRS configuration, various derivatives of QRS configuration and S-T segment or T wave evaluation. Irrespective of the exact hardware and data retrieval techniques used, manual systems are all potentially limited by operator fatigue. New commercial systems are becoming available that are more automated and that provide quantitative arrhythmia analysis. When using such systems, it is important that the operator determine the accuracy of analysis.

Several techniques of computer analysis of ambulatory electrocardiographic tapes have been developed. The computer scanning is performed at 60 or 120 times real-time, with periods of abnormality located and then printed as standard electrocardiographic samples for later physician analysis. These systems permit identification of premature ventricular beats, quantitation of arrhythmia frequency and printout of summary data relating to their frequency and complexity. The best described systems have been developed at Washington University[1–3] and Stanford University,[4–6] although a large number of other systems have been developed at institutions in Europe and the United States. At Stanford we have developed two techniques of analysis during the past 7 years and have used them for studying patients with cardiac arrhythmias. Both of these systems have been used to determine the effectiveness of antiarrhythmic drugs. Between 1970 and 1975 we used an analog preprocessor that identified features of each QRS and presented these extracted features to a digital

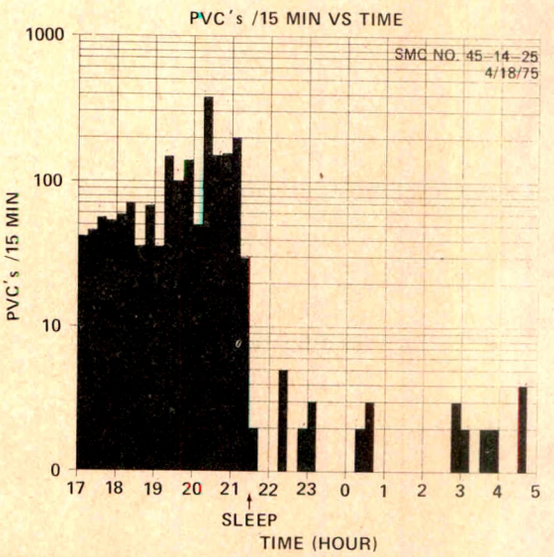


FIGURE 1. Quantitative graphic computer printout of premature ventricular complex (PVC's) frequency versus time. Frequency per 15 minutes (PVC's/15 MIN) ranged from 29 to 285 during the first 4 1/2 hours. The patient then went to sleep and the premature complexes became very infrequent. (Reprinted with permission of Harrison et al. and *The New England Journal of Medicine*.[46])

computer for analysis.[4,5] On the basis of prematurity, duration of QRS complex and a mathematical representation of the vector of the QRS complex, beats were classified as normal or premature ventricular complexes and their numbers were quantitated (Fig. 1). Since 1975 we have developed a system that permits correlation of each QRS complex with an existing family of beats.[6] After each analysis period, the configurations of specific families of beats are displayed for the operator to review. If there is a close resemblance between individual families, they may be merged by operator interaction. These analysis systems provide powerful tools for the cardiologist to study patients and to identify premature ventricular complexes and other arrhythmias that may be important in evaluating prognostic significance or determining the effectiveness of antiarrhythmic drug therapy.

Clinical Uses of Ambulatory Electrocardiographic Monitoring

Ambulatory electrocardiographic monitoring has three potential uses with regard to antiarrhythmic drug therapy. (1) Its first use is to detect cardiac arrhythmias. Studies utilizing ambulatory monitoring have determined that a large number of cardiac arrhythmias produce no symptoms. Conversely, a large number of symptoms experienced by patients with and without heart disease, which are suggestive of cardiac arrhythmias, occur at times when no cardiac arrhythmias are detected on ambulatory electrocardiographic monitoring.[7,8] (2) The second use is to provide prognostic information about the arrhythmia and the need for therapy. When arrhythmias are detected on ambulatory electrocardiograms, the physician must determine the meaning of the arrhythmias. Arrhythmias can be present even in apparently healthy subjects,[9,10] and the prognostic meaning of many of the arrhythmias detected on ambulatory electrocardiographic monitorings is currently unknown. However, particularly in the patient population with coronary artery disease, information is now available that will aid the physician in interpreting the meaning of arrhythmias recorded on ambulatory electrocardiograms. (3) Finally, if a physician has made a decision to treat a cardiac arrhythmia, the ambulatory recordings are a potential aid for evaluating the effectiveness of drug therapy.

In the sections that follow we will discuss the use of ambulatory electrocardiographic monitoring for detecting arrhythmias, deciding on the need for therapy and evaluating therapy. We cannot emphasize too strongly that physicians using ambulatory electrocardiographic monitoring in the clinical setting should discard any preconceived ideas or ideas based on inpatient and coronary care unit data that they may have concerning (1) what is normal or abnormal in ambulatory electrocardiograms, (2) the prognostic significance of these recorded arrhythmias, and (3) how the recording should be used to assess the effectiveness of antiarrhythmic drug therapy in an individual patient. Interpretation and use of these ambulatory recordings with regard to these points should be based solely on available published data. It must also be emphasized that in many instances the answers to the questions outlined are unavailable at present. However, a large number of studies are under way at many medical centers, and it is hoped the answers will be forthcoming in the next few years.

Arrhythmias in Normal Subjects

Little information is available about the spectrum of arrhythmias detected on ambulatory electrocardiographic recordings and their prognostic implications in subjects free of clinical evidence of heart disease. In a group of 37 normal men with a median age of 39 years, Gilson[11] found ventricular ectopic beats to be a rarity. In another study he detected ventricular ectopic beats in ambulatory electrocardiograms in only 4 of 65 normal subjects.[12] In that study, all but four subjects were less than 55 years of age. Brodsky et al.[10] recently reported the ambulatory electrocardiographic recording findings in 50 male medical students without cardiovascular disease. They found that 56 percent of medical students had atrial premature beats; however, only one had more than 100 such beats in 24 hours. Fifty percent of the students had premature ventricular complexes, but again only one had more than 50 such complexes in 24 hours. Fifty percent of the subjects had marked sinus arrhythmia with spontaneous changes in adjacent cycle lengths of 100 percent or more, and 28 percent of the subjects had sinus pauses of more than 1.75 seconds (usually during sinus arrhythmia). Transient nocturnal type I second degree heart block was noted in three subjects. From these studies it must be concluded that, although occasional atrial or ventricular premature beats are common in younger populations, frequent ectopic beats and complex patterns appear to be uncommon. Bradyarrhythmias, including marked sinus arrhythmia and sinus bradycardia, appear to be a common finding.

In another study, Clark et al.[9] studied 86 subjects with 48 hours of ambulatory electrocardiographic monitoring. In this apparently normal population, ranging in age from 16 to 65 years, they found 12 percent of the subjects to have disturbances of rhythm that are widely believed to be of serious prognostic significance. These included frequent ventricular ectopic beats, R-on-T multifocal ventricular beats, bigeminy and ventricular tachycardia. They also noted other rhythms, including supraventricular tachycardia, infrequent ventricular beats, junctional rhythm and second degree heart block. These authors concluded that apparently normal subjects can have a wide range of disturbances of cardiac rhythm. However, in each of these studies it must be stressed that the appearance of these rhythms in an apparently normal population does not necessarily make them normal. Only long-term follow-up of such apparently healthy patients will determine the importance of these arrhythmias.

A frequently quoted study evaluating rhythm disturbances in an unselected patient population is that of Hinkle et al.[13] In 301 men with a median age of 55 years, they detected supraventricular arrhythmias in

TABLE I

Ventricular Arrhythmias Detected in Ambulatory Electrocardiograms as Predictors of Subsequent Cardiac Events in Patients With Coronary Artery Disease

Reference	Population	Patients (no.)	Cardiac Event	Duration and Frequency of Monitoring	Predictive Arrhythmias
Kleiger et al.,[16] Oliver et al.[17]	2 wk–18 mo post MI	141	. . .	10–24 hr every mo	Frequent PVCs
Kotler et al.[18]	≥3 mo post MI	160	Sudden death	12 hr at least every 8 mo	Frequent PVCs (>10/hr) or complex ventricular arrhythmia except parasystole
Moss et al.[19]	3 wk post MI	100	Sudden death	One 6 hr recording	PVC frequency, bigeminy or in pairs
Moss et al.[20]	Before hospital discharge	193	Sudden death, reinfarction	One 6 hr recording	>20 PVCs/hr, multiform or bigeminal PVCs
Vismara et al.[21]	11 days post MI	64	Sudden death	One 10 hr recording	Presence of ventricular arrhythmias as especially complex forms
Ruberman[22]	Post MI: 50% <3 mo 30% 3–8 mo 20% >9 mo	1739	Sudden death	One 1 hr recording	Complex PVCs (R on T, two or more, multiform, bigeminal)

MI = myocardial infarction; PVC = premature ventricular complex.

76 percent and ventricular arrhythmias in 63 percent. In that study, the risk of sudden death during a 5 year period of follow-up was greater in those patients with premature ventricular complexes who had more than 10 per 1,000 complexes than in subjects without this finding. This study, however, cannot be taken as reflective of normal, since on entry into the study, at least 20 percent of the patients were known or suspected to have coronary artery disease. Many of the sudden deaths occurred in this 20 percent of the patients.

Implications: We are just beginning to learn about the spectrum of conduction and rhythm disturbances that can exist asymptomatically in an unselected so-called clinically normal patient population. It is clear that a wide range of cardiac conduction disturbances and arrhythmias will be observed when large numbers of persons without evidence of heart disease undergo ambulatory electrocardiographic monitoring. This is especially true as the age of the population being monitored increases. Physicians obtaining ambulatory recordings in asymptomatic patients must interpret the findings carefully in light of these facts. It is important that antiarrhythmic drug therapy not be initiated for arrhythmias that have no known clinical significance. Ultimately, it will be important to follow up large numbers of subjects in all age groups who undergo ambulatory electrocardiographic monitoring to determine the clinical importance of each of the disturbances detected on ambulatory recordings.

Prognostic Significance of Arrhythmias in Patients With Known Coronary Artery Disease

It has been postulated that premature ventricular complexes in patients with coronary artery disease are harbingers of sudden death. Epidemiologic studies such as those carried out in Tecumseh, Michigan[14] and the Coronary Drug Project[15] have indicated that isolated premature ventricular complexes recorded in a standard 12 lead electrocardiogram increase the risk of sudden death in patients with coronary artery disease. These findings, and the study of Hinkle et al.,[13] which demonstrated that frequent premature ventricular complexes predicted among unselected patients those who were at high risk of sudden death, have stimulated interest in extensive ambulatory electrocardiographic monitoring of patients with coronary artery disease because such patients are at high risk of sudden death. Studies[16–22] that have identified arrhythmias in patients in the early postinfarction period and determined their prognostic significance are summarized in Table I. Many of these are ongoing studies, and data are continually being published to update the findings. Each of these studies suggests that the occurrence of frequent or complex ventricular arrhythmias, or both, in the early postinfarction period provides important prognostic information with regard to the risk for sudden death.

In another recent study, Ruberman et al.[22] examined the prognostic value of 1 hour of electrocardiographic recording in a group of patients with a history of myocardial infarction that was not necessarily recent. Complex premature beats were defined as those occurring on the T wave, in runs of two or more, with a multiform or bigeminal pattern. They noted that the presence of any complex beats during the recorded hour significantly increased the patient's risk of sudden cardiac death. Approximately three fourths of all patients with complex premature beats in their recorded electrocardiogram also had frequent ectopic beats, defined as more than 10 such beats in the recorded hour. Of note in that study was the finding that simple ventricular premature beats only, even when they are frequent, did not significantly increase the risk of sudden coronary death. An attempt to determine the prognostic value of each type of complex ventricular beat was dif-

ficult because of the strong associations found among the four specified characteristics defining complex beats. It was determined, however, that patients with R-on-T phenomenon or runs of ventricular beats were at considerably greater risk than those with multiform or bigeminal beats.

Ventricular ectopic beats as harbinger of sudden death: Although the exact criteria used to define complex beats and frequent ectopic beats vary somewhat among the preceding studies, there appears to be near uniform agreement that the presence of ventricular ectopic beats that are frequent or complex, or both, in patients with previous myocardial infarction identifies the patient who is at increased risk of subsequent sudden cardiac death. These studies have varied in duration of recording period from 1 to 24 hours. The most appropriate duration of monitoring of such patients to detect those at high risk of subsequent cardiac death is still unclear. Because previous studies, and our experience, have indicated that the longer one monitors a patient the more likely one is to detect complex forms, it is quite possible that the longer recording periods will detect a greater percentage of patients with complex forms. However, by monitoring for longer periods, one may be detecting patients whose risk is not increased to as great a degree as those in whom complex forms are recorded during the 1st hour only. Finally, it must be pointed out that even among patients free of complex or frequent arrhythmias the rate of sudden cardiac death is not insignificant in the early postmyocardial infarction period.

Arrhythmias in Other Cardiovascular Conditions

Ambulatory recordings have provided a better understanding of the spectrum of arrhythmias in a number of cardiac syndromes such as mitral valve prolapse,[8,23] sick sinus syndrome, idiopathic hypertrophic subaortic stenosis,[24] Wolff-Parkinson-White syndrome,[7,25] chronic pulmonary disease[26] and bradycardia-tachycardia syndrome, as well as in patients who have undergone cardiac transplantation.[27] In most patients with these conditions the occurrence and frequency of arrhythmias appear to exceed those that would be found in a normal patient population. However, in most conditions other than mitral valve prolapse,[23] a careful comparison with a control group has not been performed, and in none of these conditions is the prognostic significance of the arrhythmias known.

Arrhythmias and Symptoms

Ambulatory recordings have made physicians aware that many symptoms suggesting cardiac arrhythmias occur in the absence of such arrhythmias, and many cardiac arrhythmias, some of which have important prognostic information, occur without symptoms. Before initiating antiarrhythmic therapy, it is frequently important to know the relation between symptoms experienced by the patient and the presence or absence of cardiac arrhythmias. Patients with palpitation should undergo monitoring to determine whether or not an arrhythmia is responsible for the symptoms. If an arrhythmia is documented as the cause of palpitation the exact type of arrhythmia can be identified and appropriate therapy can be initiated. If no arrhythmias are found, inappropriate antiarrhythmic therapy can be avoided. Patients with unexplained syncope should also undergo ambulatory electrocardiographic monitoring because arrhythmias may be found that can explain the patient's symptoms.[28,29] Caution must be urged when interpreting asymptomatic arrhythmias manifested in an ambulatory electrocardiogram in a patient with intermittent symptoms. To be certain of cause and effect, the symptoms and arrhythmias must occur simultaneously. However, when no other cause for the symptoms can be found, the asymptomatic arrhythmias recorded in the ambulatory electrocardiogram may provide a clue to the etiology of the symptoms. In our experience, the less frequently the symptoms occur the less likely one is to obtain useful information from the ambulatory electrocardiogram. When symptoms occur daily, or almost daily, there is a great likelihood that the physician can determine whether they are due to a cardiac arrhythmia and will be able to identify the responsible arrhythmia.

Spontaneous Variation of Arrhythmias

The widespread use of ambulatory monitoring has uncovered a rather striking spontaneous variation in the number and complexity of premature ventricular beats that may occur in an individual patient.[30,31] When ambulatory electrocardiograms are recorded on multiple days or at varying intervals in individual patients there can be such large differences in the total number and complex types of ventricular ectopic beats that antiarrhythmic drug effect or drug-induced worsening of cardiac arrhythmias can be simulated. Using ambulatory electrocardiographic recordings, we have demonstrated that there can be short-term as well as long-term spontaneous variation, each of which can complicate the evaluation of antiarrhythmic drug therapy.

In a study involving 20 patients with frequent premature ventricular beats, Winkle[30] examined the spontaneous variation in arrhythmias during a 6 hour ambulatory recording. The study simulated the conditions of acute antiarrhythmic drug testing, where a brief control period is obtained and antiarrhythmic response is determined after a single large oral dose of an antiarrhythmic drug. However, in that study no drug was given. It was noted that spontaneous variation in ventricular arrhythmias in individual patients frequently mimicked antiarrhythmic drug effect. Another study[31] examined the antiarrhythmic effects of procainamide, quinidine and propranolol, using 24 hour ambulatory monitoring before antiarrhythmic drug therapy and a final control monitoring at the end of the study 1 month after the initial control monitoring. This study demonstrated a wide range of spontaneous variation from the initial control 24 hour monitoring to the final one. This spontaneous variation was so great that it frequently was of the same magnitude as the reduction in arrhythmias seen in these patients when they were

taking the antiarrhythmic drugs. In both of these studies, spontaneous reduction in arrhythmia from one control period to the next in the range of 50 to 90 percent occurred frequently. Spontaneous reductions greater than 90 percent were infrequent although they did occur occasionally. Spontaneous increases in the total number of ectopic beats of up to several hundred percent also occurred.

Antiarrhythmic drug response versus spontaneous variation: Thus, with a single isolated ambulatory electrocardiographic recording it is frequently difficult for a physician to determine whether a patient is in a low or a high phase of his arrhythmia. Lack of such information can cause important errors to be made when assessing antiarrhythmic drug therapy based on ambulatory monitoring. This was noted in a recent study by Winkle et al.[32] evaluating the long-term efficacy of a new antiarrhythmic drug, tocainide. An initial control ambulatory electrocardiographic recording was obtained before drug administration. Administration of the antiarrhythmic drug was then begun and ambulatory recording was repeated; the second recording showed considerably fewer premature ventricular beats than were seen in the control tape. This finding was interpreted as suggesting an antiarrhythmic drug effect and the patient was continued on long-term drug therapy. Periodically during the next year, ambulatory electrocardiographic recordings were obtained both during tocainide therapy and in its absence. It became apparent that the initial presumed antiarrhythmic response for some patients was merely spontaneous variation, and after multiple recordings were obtained both with and without antiarrhythmic drug therapy, sustained antiarrhythmic drug action could not be documented (Fig. 2).

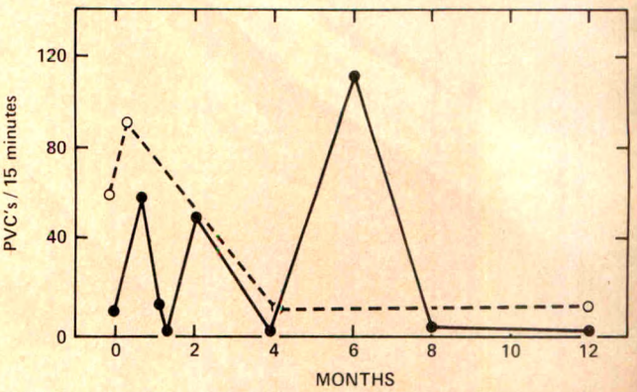


FIGURE 2. Spontaneous variation of premature ventricular complexes (PVC's) shown in sequential ambulatory electrocardiographic monitoring in a patient being treated with a new oral antiarrhythmic agent, tocainide. Each data point represents the average number of premature complexes per 15 minutes in an 8 hour ambulatory electrocardiographic recording. **Open circles** represent data obtained during periodic withdrawals of tocainide and **closed circles** represent data obtained while the patient was receiving tocainide. The initial control recording showed 58 premature complexes per 15 minutes and the initial tocainide recording only 9 per 15 minutes (an 85 percent decrease), suggesting drug effect. However, subsequent recordings in the presence and absence of tocainide suggested that this patient had a large amount of spontaneous variation in frequency of premature ventricular complexes and that the initial apparent response was a spontaneous decline mimicking antiarrhythmic drug effect. (Reprinted with permission of Winkle et al.[32] and the American Heart Association, Inc.)

Our experiences with multiple ambulatory electrocardiographic recordings in the same patient suggests not only that the total number of ectopic beats is highly variable, but also that the occurrence of some types of complex beats can be extremely variable.[30,31] Such events as brief runs of ventricular tachycardia may occur only infrequently and may ultimately prove to be even less reproducible than the total number of ectopic beats. Thus the presence or absence of an occasional run of ventricular tachycardia or other complex form in an ambulatory electrocardiogram should not be taken as the sole criterion for judging drug efficacy or its lack.

Who Should Receive Antiarrhythmic Drug Therapy?

Arrhythmias in symptomatic patients: The ambulatory electrocardiogram has proved an excellent tool for identifying arrhythmias in patients with and without heart disease and for correlating these arrhythmias with symptoms experienced by the patient. However, when arrhythmias are detected in an ambulatory electrocardiogram, the physician must then decide whether these arrhythmias require therapy. When the arrhythmias are associated with significant symptoms that are troublesome to the patient, the need for therapy is usually apparent. When repeated ambulatory monitoring has confirmed that the patient's symptoms are a reliable index to the occurrence of arrhythmias, we have generally taken elimination of symptoms as the end point of therapy.[33] For patients with recurrent sustained or symptomatic ventricular tachycardia, or both, repeated follow-up ambulatory monitoring in patients whose drug therapy renders them asymptomatic frequently continues to show asymptomatic ventricular irritability, including occasional brief runs of ventricular tachycardia.[33] Because we have found that it is difficult to suppress all asymptomatic arrhythmias with any antiarrhythmic drug in such patients, or that the high level of drug therapy necessary to do so produced intolerable side effects, we generally do not change therapy for asymptomatic arrhythmias that we detect on subsequent follow-up ambulatory electrocardiograms and do not necessarily even obtain such recordings.

Arrhythmias in asymptomatic patients: When arrhythmias are detected in ambulatory electrocardiograms in asymptomatic patients, the decision for therapy is much more difficult. With the exception of results observed in patients with prior myocardial infarction who have ventricular premature beats that are frequent or complex, or both, there is no evidence to suggest that any asymptomatic arrhythmia detected in an ambulatory recording has ominous prognostic implications for the patient. This does not mean that the arrhythmias may not have such prognostic importance, but that no prognostic studies have been performed to date for arrhythmias detected in most clinical syn-

dromes. For patients with coronary artery disease it is clear that ventricular irritability that is frequent or complex, or both, identifies the patient at increased risk of subsequent sudden death. However, even in this patient group, it is still uncertain whether therapy with antiarrhythmic drugs will alter the prognosis. Encouraging preliminary studies using the beta blocking drugs practolol[34] and alprenolol[35,36] have indicated that drug therapy may reduce the occurrence of sudden death in patients who have had a myocardial infarction. However, these studies provide no data to determine whether therapy will be effective only in those patients with ventricular irritability or whether suppression of asymptomatic ventricular ectopic beats is necessary to effect a reduction in sudden cardiac death. Until such answers are forthcoming from large multicenter intervention trials utilizing ambulatory electrocardiographic recordings, each physician must make his own decision as to which of his patients with coronary artery disease should be treated and what the end point of therapy should be.

Monitoring Antiarrhythmic Drug Therapy With Ambulatory Electrocardiograms

Our clinical experience as well as most previously reported experience is limited primarily to monitoring the therapy of ventricular arrhythmias, and the following discussion therefore deals primarily with these arrhythmias.

Monitoring therapy in individual patients: As mentioned, for patients with major symptomatic arrhythmias whose symptoms and sustained arrhythmias are well correlated and whose symptoms are suppressed by drugs, there appears to be little need for subsequent ambulatory electrocardiographic monitorings. We have been satisfied with the elimination of major symptomatic arrhythmias as an end point of therapy that can be achieved in many patients.[33] Total suppression of all asymptomatic ventricular irritability is a goal that frequently cannot be accomplished with currently available antiarrhythmic drugs. In our experience, obtaining multiple sequential recordings in patients with major symptomatic sustained ventricular tachycardia has had the effect of tempting physicians to discontinue the therapy that effectively controlled these sustained episodes because recordings revealed the occurrence of three or four beats of asymptomatic ventricular tachycardia or frequent or multifocal premature ventricular contractions.

For asymptomatic patients who manifest ventricular arrhythmias in ambulatory electrocardiographic recordings, there is no evidence to suggest that suppression of the asymptomatic ventricular irritability will influence the patient's risk of sudden cardiac death. However, because it is likely that antiarrhythmic therapy may be able to influence subsequent sudden cardiac death when given to patients in whom arrhythmias indicate an increased risk, many physicians desire to suppress asymptomatic ventricular irritability in patients with coronary artery disease. In many such patients, the occurrence of large spontaneous variations in arrhythmia makes it extremely difficult to evaluate antiarrhythmic drug efficacy.[32] One must obtain control ambulatory monitorings before initiating drug therapy. Therapy should then be given, with initial doses of antiarrhythmic drugs based on known pharmacokinetics for the drug of choice. Such data would include bioavailability, distribution of the agent, effective plasma concentrations necessary to produce effect and plasma concentration half-life times. When the patient is receiving an adequate dose of an antiarrhythmic drug, ambulatory monitorings may be repeated to determine the effect on the ventricular irritability.

From our present experience with individual patients, it is apparent that one must produce nearly total suppression of arrhythmia to be certain one is measuring antiarrhythmic effect rather than a spontaneous reduction of arrhythmia. Such certainty requires at least 90 percent arrhythmia suppression in most instances.[30,31] It must be recognized that if one sees less dramatic reduction, one may still be dealing with antiarrhythmic drug effect. Conversely, if one sees an increase in arrhythmias one need not necessarily attribute this to drug-induced worsening of arrhythmias because spontaneous variation alone can account for the increase. However, if this increase can be reliably reproduced or is associated with the development of new or changing symptoms, it is prudent to associate it with

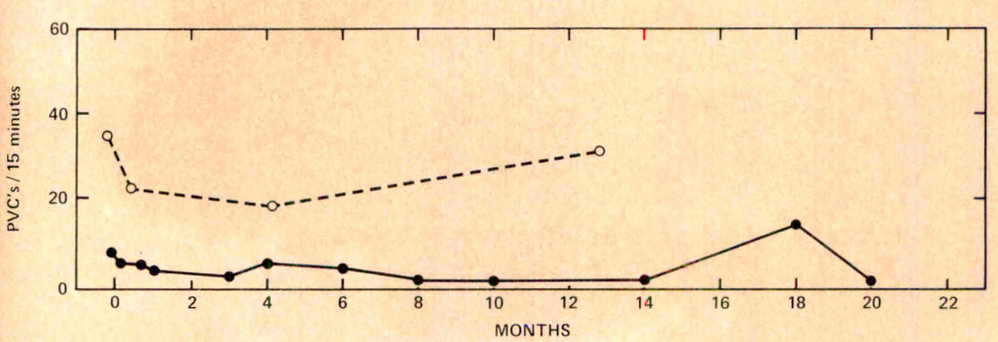


FIGURE 3. Continuing drug efficacy documented with ambulatory electrocardiography. The format is similar to that of Figure 2 with **open circles** representing frequency of premature ventricular complexes (PVC's) during periodic drug withdrawals interspersed with recordings obtained during tocainide therapy **(closed circles).** Such sequential monitoring is extremely expensive but is able to document ongoing drug efficacy. (Reprinted with permission of Winkle et al.[32] and the American Heart Association, Inc.)

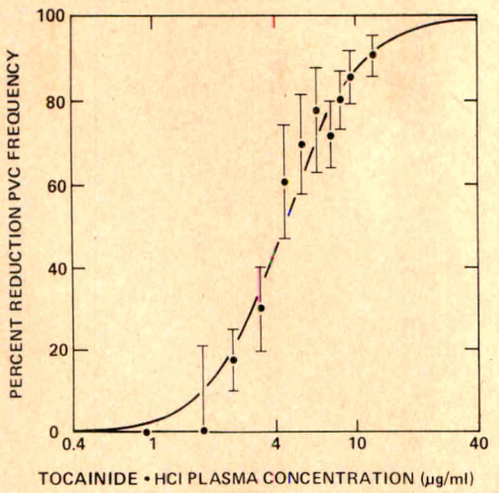


FIGURE 4. Concentration-response curve for tocainide obtained by relating reduction of premature ventricular complexes (PVC) in ambulatory electrocardiographic recordings to plasma tocainide concentration. (Reprinted with permission of Winkle et al.[37] and the American Heart Association, Inc.)

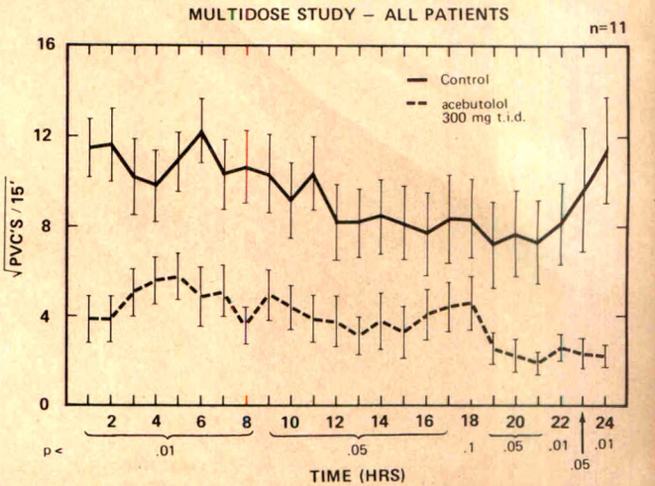


FIGURE 5. Analysis of group 24 hour arrhythmia data from ambulatory electrocardiograms. The **upper solid curve** shows the frequency of premature ventricular complexes ($\sqrt{PVC'S/15'}$) for 11 patients during the control period. The **lower dashed curve** shows the frequency during therapy with 300 mg of acebutolol three times daily (t.i.d.). The group as a whole showed statistically significant reduction of premature ventricular complexes during almost all hours. (Reprinted with permission of Gradman et al.[39] and the American Heart Association, Inc.) n = number of patients; p = probability.

drug treatment. If a patient shows nearly complete arrhythmia suppression the therapy can be judged as probably effective. The patient would then need to undergo periodic sequential ambulatory monitorings to document continuing efficacy of the drug regimen. In order to be absolutely certain scientifically that the drug is continuing to be efficacious, the patient would need to have periodic drug withdrawals, with control monitorings in the absence of all drugs interspersed throughout the period of follow-up[32] (Fig. 3). Unfortunately these periodic drug withdrawals result in periods without antiarrhythmic drug protection.

In our experience it is quite unlikely to have sustained total arrhythmia suppression, and occasional complex ventricular irritability should not be taken as a sign of lack of drug effectiveness, especially if such forms are extremely frequent in the control recordings. Such intensive ambulatory monitoring of antiarrhythmic drug therapy is too expensive and impractical to recommend for large numbers of patients. However, at the present time we know of no other way to document ongoing efficacy in individual patients with asymptomatic ventricular irritability.

Use of Ambulatory Electrocardiographic Monitorings for Antiarrhythmic Drug Trials

Ambulatory monitorings have been widely used for evaluating currently used and new antiarrhythmic drugs.[37–46] This has been one of the most important contributions of ambulatory electrocardiographic recordings to antiarrhythmic drug therapy. These recordings have provided the first available objective method for assessing antiarrhythmic drug efficacy. Not only have they permitted documentation of efficacy, but also appropriately designed studies allow correlation of antiarrhythmic drug effects (measured from ambulatory electrocardiographic recordings) with drug plasma concentration[37,38] (Fig. 4). When one is designing an antiarrhythmic drug trial, it is important to take into account the role of spontaneous variation of arrhythmias. For many types of clinical trials this spontaneous variation makes it most appropriate to evaluate antiarrhythmic drug response in a group as a whole rather than identifying individual responders and nonresponders.[30] Presumably, if one analyzes data for the group as a whole, as many patients will be having spontaneous increases as are having spontaneous decreases in their arrhythmias on any given day. Thus, any group reduction in arrhythmias can be attributed to the antiarrhythmic drug being evaluated (Fig. 5). This method assumes that arrhythmias for the group are stable throughout the course of the study. Studies such as those in the postinfarction period, in which arrhythmias may not be stable throughout the course of the study, must compare ambulatory electrocardiographic recordings in the treatment group with those in an appropriate placebo-treated group to assess the efficacy of drug therapy.

An alternative approach to group data analysis is to obtain large amounts of control ambulatory electrocardiographic data and to define the variability from hour to hour and day to day for individual patients or for the group of patients being studied. Using these data one may define statistical limits for significant arrhythmia reduction in individual patients and may separate nonresponders from reponders. This course requires many more recordings and analyses than are generally used and seems impractical until the variability of arrhythmias is better defined.

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New Antiarrhythmic Agents

Amiodarone, Aprindine, Disopyramide, Ethmozin, Mexiletine, Tocainide, Verapamil

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The present status, clinical experience, side effects, clinical pharmacology and electrophysiologic actions of seven new antiarrhythmic agents are reviewed. The drugs selected for comment are amiodarone, aprindine, disopyramide, ethmozin, mexiletine, tocainide and verapamil. Each drug has been shown to have clinical efficacy in suppressing cardiac arrhythmias.

In this review article on new antiarrhythmic agents, we have selected the following drugs for comment: amiodarone, aprindine, disopyramide, ethmozin, mexiletine, tocainide and verapamil. The discussion is limited to these seven agents because we have had clinical or laboratory experience, or both, with each of them, their mechanisms of action cover a fairly wide spectrum and, most important, each appears to be a promising candidate for approved clinical use in the United States sometime in the future. Disopyramide (Norpace®) has already been approved. We will briefly deal with the present status, clinical experience, side effects, clinical pharmacology and electrophysiologic actions of each agent. Emphasis will be placed on clinically-related information.

Amiodarone

Status: Amiodarone (Fig. 1), a benzfuran derivative with an antagonistic effect on sympathetic nerve action, is used clinically in Europe (Cordarone, Labaz Laboratory) and South America (Atlansil, Roemmers Laboratory). It has not been approved for general investigational use in the United States.

Clinical experience: Early clinical use of amiodarone was to treat angina pectoris in patients with ischemic heart disease. The drug appeared to be moderately successful for this purpose.[1] Its major clinical application has been for the therapy of both supraventricular and ventricular cardiac arrhythmias, and several noncontrolled studies support amiodarone's efficacy as an antiarrhythmic agent.[2–11]

Rosenbaum et al.[12] reported the remarkable ability of amiodarone to suppress completely tachyarrhythmias associated with the Wolff-Parkinson-White syndrome, and this early experience was confirmed by other investigators,[13–16] who also noted success, though not as great as that reported by Rosenbaum et al.

Rosenbaum et al.[17] also demonstrated the ability of amiodarone to suppress a wide variety of tachyarrhythmias in patients with different types of heart disease. They achieved "total suppression and control" of supraventricular arrhythmias in 98 of 106 patients (92.4 percent) and of ventricular arrhythmias in 119 of 145 patients (82 percent). Although the major clinical experience has been obtained from treating adults, amiodarone has been used in children with "good or moderately good" results in 88 percent of cases.[18]

We have had experience with five patients who received amiodarone (unpublished observations). Each patient had a tachycardia refractory

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TABLE I

Clinical Characteristics

Drug	Dose		Effective Serum or Plasma Concentration (μg/ml)	Elimination Half-Life (hr)	Absorption	Metabolism Secretion Route	Side Effects	Onset of Action	
	Intravenous	Oral						Intravenous (min)	Oral (hr)
Amiodarone	5–10 mg/kg	Maintenance: 200–800 mg	. . .	. . .	Fair	. . .	Ophthalmologic, endocrine, neurologic, dermatologic, cardiovascular	5–10 min	4–6
Aprindine	200 mg at 2 mg/min; 30 min later, 100 mg at 2 mg/min; 6 hr later, 100 mg at 2 mg/min	Loading: 100 mg q 6 hr, day 1; 75 mg q 6 hr, day 2; 50 mg q 6 hr, day 3. Maintenance: 25–50 mg q 8 hr or q 12 hr	1–3	20–30	Good	Hepatic	Neurologic, gastrointestinal, hematologic, cardiovascular	5–10	2
Disopyramide	2 mg/kg	Loading: 300 mg. Maintenance: 150 mg q 6 hr	2–8	5–8	Good	Renal 50%, Probably hepatic 50%	Anticholinergic cardiovascular	<5 min	½–3
Ethmozin	Loading: 1–3 mg/kg*	Maintenance: 75–150 mg, q 6 hr†	0.5–1	5–10†	Good*	Probably hepatic*	Neurologic, gastrointestinal, cardiovascular	<5*	2*
Mexiletine	Loading: 1200 mg/12 hr; Maintenance 250–500 mg/12 hr	Loading: 400–600 mg. Maintenance 200–300 mg, q 8 hr	0.5–2.0	10–26	Good	Probably hepatic	Neurologic, gastrointestinal, cardiovascular	<5	1–2
Tocainide	0.5–0.75 mg/kg per min for 15 min	Loading: 400–600 mg. Maintenance: 400–800 mg, q 8 hr	3.5–10	10–17	Good	Renal 40%, Probably hepatic 60%	Neurologic, gastrointestinal, cardiovascular	5–10	1½
Verapamil	0.075–0.15 mg/kg	Maintenance: 80–120 mg q 8 hr or q 6 hr	. . .	3–7	Good	Hepatic	Neurologic, gastrointestinal, cardiovascular	<5	1–2

* Animal data.
† According to studies in progress, maintenance doses may be in the range of 250 mg every 8 hours and provide a slightly longer half-life.
q = every.

to all conventional drugs plus a variety of experimental agents, including aprindine, mexiletine and tocainide. Amiodarone failed to control the tachyarrhythmias in two patients, one with an ectopic, automatic supraventricular tachycardia of unknown origin and one with recurrent ventricular tachycardia and ventricular fibrillation due to a cardiomyopathy. Amiodarone successfully suppressed recurrent ventricular tachycardia in the remaining three patients, two with probable cardiomyopathy and one with coronary artery disease.

Side effects: Although amiodarone is very well tolerated and results in a small incidence of gastrointestinal problems such as constipation or nausea and vomiting, it may be responsible for a variety of more distressing problems. Amiodarone may cause a peculiar slate-grey or bluish discoloration of the skin[19,20] which may take many months to disappear when the drug is stopped. Electron microscopic studies have revealed histiocytes containing granules that had histochemical properties of melanin and lipofuscin.[21–23]

Amiodarone may also cause thyroid dysfunction, and patients may manifest hypo-[24] or hyperthyroidism.[25] Following therapy with amiodarone, the protein bound iodine and thyroxine (T_4) levels rise while triiodothyronine (T_3) falls.[26,27] Occasionally, neurologic side effects may result.[28,29]

The most consistent complication following amiodarone therapy is the development of corneal microdeposits,[30–34] which present as a peculiar yellow-brown granular pigmentation in the cornea. With electron microscopic studies, numerous lysosomal inclusions, most probably lipofuscin, have been seen in the cytoplasm of the basal and intermediary cells of the cornea.[32] The microdeposits are reversible after cessation of therapy, and may be minimized or prevented by discontinuing drug administration periodically or by the use of eye drops. Generally, these deposits do not interfere with vision.[17]

Clinical pharmacology (Table I): Amiodarone is reported to be slowly and fairly well, though somewhat variably absorbed (about 50 percent) resulting in "low blood levels."[35] Amiodarone or its metabolites became deposited in many organs.[35] The half-life has not been determined, though it has been estimated that the body concentration has diminished by only 16 to 34 percent 30 days after administration of the drug has been stopped.[35] Such "body stores" may, in part, explain the persistence of amiodarone's antiarrhythmic effect for as long as 30 to 45 days after drug administration has been discontinued.[17] The drug may require days to several weeks for its full antiarrhythmic efficacy to become manifest.[17]

The median lethal dose (LD_{50}) of amiodarone is reported to be more than 10 times the therapeutic dose when the drug is given intravenously and even greater when given orally.[36] The presence of atrioventricular (A-V) or intraventricular block offers a relative contraindication to drug administration.[17]

Amiodarone exhibits a noncompetitive blockade of both alpha and beta adrenergic receptors[37–39] and also

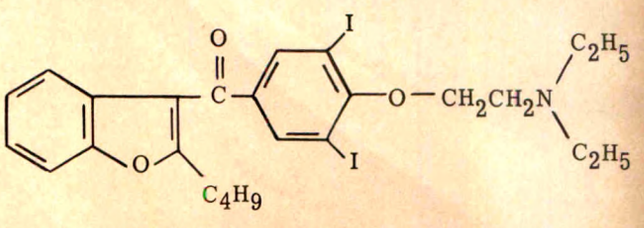


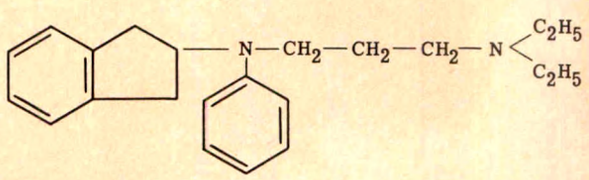
FIGURE 1. Chemical structure of amiodarone.

antagonizes the chronotropic and inotropic effects of glucagon.[38] It increases coronary blood flow, but reduces cardiac work and oxygen consumption as well as peripheral vascular resistance.[37,38] In man,[40] amiodarone (5 mg/kg intravenously) did not affect cardiac contractility but decreased peripheral resistance; at a higher dose level (10 mg/kg intravenously), amiodarone reduced left ventricular contractility and elevated left ventricular end-diastolic pressure from 6 to 13 mm Hg.

Electrophysiology (Table II): Amiodarone has been shown to suppress arrhythmias induced experimentally by barium chloride, myocardial ischemia, acetylcholine, aconitine or digitalis.[41] It slowed the sinus nodal discharge rate in anesthetized dogs even after pretreatment with propranolol and atropine.[38] In the isolated rabbit sinus node preparation,[42] amiodarone increased action potential duration and decreased the slope of diastolic depolarization. Amiodarone also prolonged the action potential duration of rabbit atrial and ventricular muscle[37] and Purkinje fibers,[17] without altering resting membrane potential or automaticity. In man,[13,43–45] amiodarone (5 to 10 mg intravenously) slowed sinus nodal discharge rate, lengthened A-V nodal conduction time, increased atrial and ventricular monophasic action potential duration and refractory periods. It increased the effective refractory period of the accessory pathway in patients with the Wolff-Parkinson-White syndrome, more often in an anterograde than in a retrograde direction.[13]

Aprindine

Status: Aprindine (Fig. 2) (Fiboran,® AE Christiaens Co.; Fibocil,® Eli Lilly & Co), an antiarrhythmic agent with prominent local anesthetic effects, was developed and used initially in Belgium. It is available clinically throughout most of Europe and is being evaluated as an



N-[3-(diethylamino)propyl]-N-phenyl-2-indanamine $C_{22}H_{30}N_2$

FIGURE 2. Chemical structure of aprindine.

TABLE II

Electrophysiology Characteristics*

	Human Studies										
	Sinus	Intervals					FRP	ERP	RRP	ERP	ERP	ERP
Drug	Rate	P-R	QRS	Q-T	A-H	H-V	AVN	AVN	HPS	HPS	A	V
Amiodarone	↓	0	0	↑	↑	0	↑	↑	↑	↑	↑	↑
Aprindine	↓	↑	↑	0↑	↑	↑	↑	↑	↑	↑	↑	↑
Disopyramide	0↑	0	0↑	0↑	0	0↑	0	0↓	↑	↑	↑	↑
Ethmozin	0↓	0↑	0↑	0								
Mexiletine	0	0	0	0	0↑	0↑	0↑	0↑	0↑	0↑	0	0
Tocainide	0↓	0	0	0↓	0↑	0	0↓	↓			↓	↓
Verapamil	↓	↑	0	0	↑	0	↑	↑	0	0	0	0

* Results presented may vary according to tissue type, experimental conditions, and drug concentration. Animal data are from "fast-response" type fibers.

↑ = increase; ↓ = decrease; 0 = no change; 0↑ or 0↓ = slight increase or slight decrease, respectively.

A = atrium; Anes = local anesthetic effects; APA = action potential amplitude; ADP = action potential duration; AVN = A-V node; CA^{++} current

investigational agent at a number of centers in the United States.

Clinical experience: Early studies[46–54] established aprindine as an effective antiarrhythmic agent against a variety of supraventricular and ventricular arrhythmias that occurred in patients with different types of heart disease. Van Durme et al.[50] treated 129 patients who exhibited chronic, stable ventricular arrhythmias with orally administered aprindine (200 to 300 mg loading dose; 100 mg daily). On the basis of analysis of Holter electrocardiographic recordings obtained "continuously" during treatment in 93 patients and 5 minute electrocardiographic strips obtained three times daily in 36 patients, they found that aprindine totally suppressed ventricular arrhythmias in 67 percent, eliminated repetitive and multiformed premature ventricular complexes and reduced the frequency of premature ventricular complexes by 50 percent in 14 percent of patients. Ventricular arrhythmias remained unchanged or were reduced by less than 50 percent in the remaining patients. Eighty-six patients had previously been given procainamide, quinidine or beta adrenergic receptor blocking drugs with little or no success. Similar data have been obtained by other investigators.

In a recent study,[55] disopyramide (100 mg), aprindine (20 mg) or placebo in identical capsules was given to patients every 6 hours on the 4th through the 20th day after acute myocardial infarction. The presence of ventricular arrhythmias was documented by daily examination of patients, by standard electrocardiograms plus four 5 minute electrocardiographic recordings. Although the data would have been strengthened by obtaining 24 hour ambulatory recordings, on the basis of the brief recordings, Pouleur et al.[55] found that less ventricular arrhythmias occurred in the aprindine-treated group than in the disopyramide-treated group ($P < 0.05$) or in the group receiving placebo ($P < 0.05$).

Our initial experience with aprindine was reported in this Journal recently.[56] We treated 23 patients with recurrent ventricular tachycardia (10 patients) or recurrent ventricular tachycardia and ventricular fibrillation. All patients either had not tolerated or had not responded to conventional antiarrhythmic drugs or overdrive pacing. The average daily maintenance dose of aprindine was 147 mg/day, producing a mean plasma concentration of 1.7 μg/ml. All arrhythmia data were obtained from 24 hour Holter recordings. In the group with only ventricular tachycardia, aprindine prevented further episodes in eight patients, failed to prevent ventricular tachycardia in one patient and converted sustained episodes of ventricular tachycardia to short asymptomatic bursts in one patient. In the group with ventricular tachycardia and ventricular fibrillation, aprindine prevented further recurrences in all but one patient, who continued to have recurrent episodes of ventricular tachycardia. One responder had to stop the drug because of intolerable side effects. Thus, among the 23 patients, aprindine was not tolerated by one patient and failed to control the ventricular arrhythmia in two patients. In five responders, aprindine plus propranolol (one patient), aprindine plus quinidine (three patients), and aprindine plus permanent ventricular pacing (one patient) achieved better suppresssion than aprindine alone.

We have extended this initial study to include an additional 50 patients with a variety of cardiac diseases who were treated chronically for frequent symptomatic premature ventricular complexes (2 patients), recurrent ventricular tachycardia (36 patients) or recurrent ventricular tachycardia and ventricular fibrillation (12 patients) (unpublished observations). As in our first study, all patients were intolerant of, or did not respond to conventional antiarrhythmic agents, including quinidine (45 patients), procainamide (42 patients), propranolol (36 patients), lidocaine (20 patients), diphenylhydantoin (13 patients) and overdrive pacing (2 patients). The average daily maintenance dose of aprindine was 127 mg, producing a mean serum concentration of 1.8 μg/ml. Data were analyzed from 24 hour ambulatory electrocardiographic recordings. Thirteen patients discontinued aprindine because it exacerbated the ventricular tachycardia (two patients),

TABLE II (cont'd)

	Animal Studies												
Drug	APA	APD	dV/dt	MDP	ERP	Cond Vel	Normal Phase 4	Memb Resp	ET	VFT	Contractility	Ca^{++} Current	Autonomic Nervous System	Anes
Amiodarone	0	↑	0↓	0	↑	↓	0	↓			↓		Antisympathetic	No
Aprindine	0	↓	↓	0	↓	↓	↓	↓	↑	↑	↓	0	0	Yes
Disopyramide	↓	↑	↓	↓	↑	↓	↓	↓			↓	0	Antivagal	Yes
Ethmozin	↓	↓	↓	0↓	↓	↓	0	↓	↑	0	↑then↓	0	0	No
Mexiletine	0	↓	↓	0	↓	↓	↓	↓	↑	↑	↓	0	0	Yes
Tocainide	0	↓	0↓	0	↓	↓	↓	↓	↑	↑		0	0	Yes
Verapamil	0	↓	0	0	0	0	↓	0		0	↓	Inhibit	0	Yes

= slow current or slow response; Cond Vel = conduction velocity; dV/dt = rate of rise of upstroke (phase 0) of action potential; ERP = effective refractory period; ET = excitability threshold; FRP = functional refractory period; HPS = His-Purkinje system; MDP = maximal diastolic potential; RRP = relative refractory period; V = ventricle; VFT = ventricular fibrillation threshold.

failed to control the ventricular tachycardia (five patients), produced intolerable side effects (four patients), or because the ventricular arrhythmias no longer recurred (two patients). Three patients died, one with acute myocardial infarction, one with severe congestive heart failure and one with metastatic carcinoma. In the remaining 34 patients still receiving aprindine over a period of 1 to 15 months (mean 9 months), the most recent 24 hour Holter recording revealed no episodes of ventricular fibrillation or ventricular tachycardia in 30 patients and 80 percent suppression (compared with control recordings) of premature ventricular complexes. Four patients still have recurrent short asymptomatic episodes of ventricular tachycardia. One patient is receiving quinidine and aprindine. Although ischemic heart disease was the major cardiac disorder in this group, seven patients had ventricular tachycardia associated with mitral valve prolapse and all seven responded to aprindine.[57]

Aprindine has also been used to treat patients with supraventricular arrhythmias,[46,49,51,52,53,58–60] but was generally somewhat less successful in cases of ventricular arrhythmias. Recently, we[58] reported in this Journal our experience on the use of aprindine in treating 10 patients with recurrent or continuous supraventricular tachycardia difficult to control with conventional arrhythmic agents. Nine patients had Wolff-Parkinson-White syndrome. An electrophysiologic study was performed before and during oral administration of aprindine. At the time of the first study, circus movement supraventricular tachycardia was initiated in eight patients. During administration of aprindine, circus movement supraventricular tachycardia could no longer be initiated in four patients, was initiated with difficulty in two patients and with greater ease in two patients. In one patient, aprindine therapy slowed the ventricular response during atrial flutter from 1:1 conduction over the accessory pathway to 2:1 conduction over the normal pathway; in another patient, it slowed the ventricular rate during atrial fibrillation from 140–180 to 80–100 beats/min. Eight patients had an excellent clinical response, but treatment with aprindine was discontinued in two patients. Electrophysiologic evaluation revealed that aprindine produced complete block or increased refractoriness of the accessory pathway in an anterograde direction in all patients (making it an exceptionally useful drug in patients with the Wolff-Parkinson-White syndrome who experience atrial flutter or atrial fibrillation and rapid ventricular rates due to conduction over the accessory pathway), and in a retrograde direction in all but two patients tested. In the patients in whom paroxysmal supraventricular tachycardia could be initiated despite aprindine therapy, and in whom conduction during the paroxysmal supraventricular tachycardia was retrograde over the accessory pathway and antegrade over the normal pathway, the ventriculoatrial (V-A) interval, measured from the earliest onset of ventricular depolarization to the first rapid atrial deflection located on the same side as the accessory pathway, increased, indicating that aprindine resulted in slowed conduction in the ventricle or accessory pathway, or both. The tachycardia occurred at a slower rate, as expected from such changes.

We have studied an additional eight patients who experienced paroxysmal supraventricular tachycardia (unpublished observations). Four had manifest and one had concealed accessory pathway conduction, one had an A-V nodal reentry tachycardia and two had a probable automatic atrial tachycardia. Aprindine has markedly decreased or prevented a recurrence of tachycardia in five of the eight patients. One patient with Wolff-Parkinson-White syndrome and one with atrial tachycardia due to increased automaticity did not respond and the drug was discontinued. One patient with A-V nodal reentry developed tremulousness and diaphoresis after two oral doses of aprindine and administration of the drug was stopped.

Side effects: The toxic-therapeutic ratio for aprindine is rather narrow, and side effects, particularly during the initial loading period and adjustment of the maintenance dose, are quite common. If a loading dose is not given and the patient is just started on a maintenance dose, the incidence of side effects decreases.

Thirty-nine of the 50 patients with ventricular arrhythmias described earlier exhibited early side effects, primarily involving the central nervous system. These side effects, related to the dose and serum concentration of aprindine, include most commonly a tremor of the hand and fingers. As the serum concentration increases, dizziness, intention tremor, ataxia, nervousness, hallucinations, diplopia, memory impairment or seizures may also occur. Neurologic side effects are minimal or absent at serum aprindine concentrations of less than 1 μg/ml.[56] Gastrointestinal side effects are more infrequent than neurologic side effects. Seven of the 39 patients complained of nausea and one had diarrhea. Of the 34 patients with ventricular arrhythmias who have continued to receive aprindine chronically, 19 still experience mild side effects, due mainly to fine tremor of the hands or vertigo, which usually responds to meclizine.

We have used aprindine together with quinidine, propranolol or lidocaine on occasion without apparent difficulty.[56] Although the administration of a local anesthetic agent and aprindine has been reported to produce seizures,[61] we have had no problems when giving aprindine and lidocaine together. We found that one patient who received procainamide with aprindine experienced intolerable neurologic side effects at low plasma concentrations of aprindine (1.1 μg/ml). Quinidine was substituted for procainamide in this patient and the side effects disappeared.[56]

Recently, cholestatic jaundice and agranulocytosis[62] *have been reported to occur in association with the use of aprindine* and are thought to be idiosyncratic reactions as opposed to dose-related toxicity. The problems have generally occured between the 4th and 16th weeks of aprindine therapy, and with an estimated incidence of approximately 1 in several thousand based on data from Europe. In the United States, of 400 to 500 patients treated, 3 have developed agranulocytosis. Two recovered after aprindine was discontinued. One of these three patients died of ventricular fibrillation 24 hours after discontinuation of aprindine. Both complications appear to be reversible if the drug is discontinued (unpublished observations). In our studies,[56–58] one patient manifested a white blood cell count of 2,200 mm^3, with 17 percent polymorphonuclear leukocytes. Five days after aprindine had been discontinued, the patient's white blood cell count and differential had returned to normal. Transient abnormalities in liver function tests have been noted in some of our patients, but no abnormality has persisted or has led to discontinuation of the drug.

Clinical pharmacology (Table I): Aprindine is well absorbed, has high systemic availability and is 85 to 95 percent protein-bound. Approximately 95 percent of the hydroxylated metabolites undergoes glucuronidation in the liver. Sixty-five percent of aprindine and its metabolites is found in the urine with the remaining 35 percent in the feces.[49] Elimination half-life has ranged from 13 to 50 hours (mean 27.9 hours) in one study,[49] 20 to 30 hours in another[63] and 18 hours (mean) in a third.[64] The N-desethyl metabolite is present in small amounts in the plasma of patients treated chronically with aprindine and exerts some antiarrhythmic actions.[63] Clinically, the full antiarrhythmic effect of aprindine may not occur for several days, even when the drug is initially administered in a loading dose.

Hemodynamic studies have revealed that therapeutic doses of aprindine mildly depressed myocardial function.[47] In conscious dogs, aprindine (2 mg/kg) slightly and transiently depressed myocardial contractility. The degree of depression increased when an additional 3 mg/kg intravenously were given.[65] In open chest dogs, aprindine (2 mg/kg) did not significantly affect left ventricular dynamics, while increasing cumulative doses progressively reduced left ventricular pressure and its maximal first derivative (dP/dt), mean aortic pressure, stroke volume and cardiac output.[65,66] When studied in open chest pigs subjected to 75 percent occlusion of the left anterior descending coronary artery, aprindine (2 mg/kg per hour for 1 hour; 0.8 mg/kg per hour thereafter) did not significantly alter heart rate, cardiac output, stroke volume, right atrial pressure, peripheral resistance, left ventricular end-diastolic pressure, maximal dP/dt or left anterior descending coronary arterial flow.[67] At serum concentrations therapeutic for man, aprindine, in nine anesthetized pigs, did not significantly alter heart rate, cardiac output, left ventricular end-diastolic pressure or peripheral resistance. Mean arterial pressure, peak left ventricular dP/dt and maximal circumferential fiber shortening (Vmax) decreased slightly.[68] In man, aprindine (200 mg orally) slightly decreased systolic and mean aortic blood pressure during exercise in one study[69] and slightly depressed myocardial contractility when given intravenously (100 mg) in another.[70] At a total dose of 140 or 150 mg intravenously, aprindine produced a moderate and dose-related decrease in peak left ventricular dP/dt and Vmax.[71]

Electrophysiology (Table II): *In isolated cardiac preparations,* aprindine shortened the duration of the action potential and effective refractory period of Purkinje fibers; the former was shortened more than the latter.[72–74] However, in cardiac muscle fibers, action potential duration was only slightly reduced and the duration of the effective refractory period was lengthened.[72,73] The rate of rise of phase 0 was depressed, more so at rapid rates, at higher potassium levels, and to a greater degree than with comparable amounts of lidocaine.[72,74] Diastolic depolarization and spontaneous firing were depressed or abolished by aprindine. Aprindine also reduced digitalis-induced increases in potassium permeability[72] and suppressed transient depolarizations caused by acetylstrophanthidin in canine Purkinje fibers.[75] Aprindine does not appear to affect slow channel activity.[72,75]

Studies in intact dogs have revealed that aprindine, injected into the sinus nodal artery, decreased the spontaneous sinus rate and, injected into the A-V nodal artery, prolonged the functional refractory period and conduction time of the A-V node. Given intravenously (1.4, 2.8 and 4.2 mg/kg cumulative dose), aprindine prolonged the A-H interval, H-V interval, transmural

left ventricular conduction time and the effective refractory period of the ventricle.[76] Other studies[66,77] have reported similar data after intravenous administration of aprindine and it appears that aprindine slows conduction in all cardiac tissue.

Aprindine has effectively suppressed digitalis-induced arrhythmias,[78,79] including a specific type exhibiting overdrive acceleration.[80] Aprindine has been very effective against certain ischemia-induced arrhythmias, such as those ventricular arrhythmias occurring 24 hours after coronary arterial ligation.[78,79,81] Results of aprindine given intravenously immediately before coronary arterial ligation are conflicting due to differences in doses and methodology. In one study,[78] aprindine (0.5 mg/kg per min for 10 minutes) failed to protect against ischemia-induced ventricular arrhythmias and, in our study,[82] aprindine (2.86 mg/kg over 15 minutes) increased ischemia-induced conduction delay and the spontaneous development of ventricular fibrillation. When aprindine was given more slowly (2.0 mg/kg over 1 hour followed by 0.8 mg/kg over 1 hour) to pigs subjected to a 75 percent reduction in left anterior descending coronary arterial flow, it exerted an antiarrhythmic effect.[67] Aprindine has also been found to elevate the ventricular fibrillation threshold in the nonischemic canine heart but not during ischemia.[83]

Studies in man have demonstrated that aprindine increased the A-H and H-V intervals and QRS duration, increased the effective refractory period of the atria and ventricles and increased the functional and effective refractory period of the A-V node.[58,84,85] Aprindine blocked conduction in the accessory pathway of patients with the Wolff-Parkinson-White syndrome, more often and more reliably in an anterograde than in a retrograde direction.[58,59] Because of its negative dromotropic effect, we have found that when a tachycardia, either supraventricular or ventricular, recurred while a patient was receiving aprindine, the tachycardia exhibited a slower rate and was generally better tolerated than before aprindine therapy. Similar results have been noted with amiodarone.[13]

Disopyramide

Status: Disopyramide (Fig. 3) (Norpace®, G. D. Searle and Company) was synthesized in 1954 and its phosphate salt, very recently approved for general clinical use, has been studied in the United States since 1965. Disopyramide base (Rhythmodan®, Roussel) has been commercially available in Europe for 8 years.

Clinical experience: Since the late 1960's, disopyramide has been successfully used to treat patients with a variety of supraventricular and ventricular arrhythmias. Initial European studies,[86–88] later confirmed by investigations in the United States,[89–91] demonstrated disopyramide's efficacy in suppressing premature extrasystoles and tachycardias of both supraventricular and ventricular origin.

In patients with supraventricular arrhythmias, disopyramide has been used to prevent a recurrence of atrial fibrillation after electroconversion to sinus rhythm,[92] as well as to terminate paroxysmal supraventricular tachycardia, atrial flutter or atrial fibrillation of recent onset.[93,94] Disopyramide also prolongs the conduction time and the effective refractory period of the accessory pathway in patients with the Wolff-Parkinson-White syndrome and may be useful in treating arrhythmias associated with the preexcitation syndrome.[95]

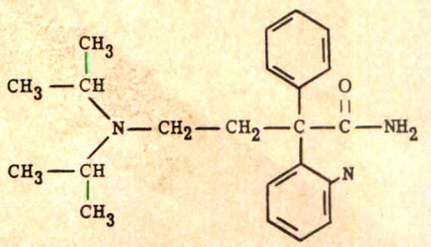


FIGURE 3. Chemical structure of disopyramide.

When administered intravenously (2 mg/kg) to 57 patients with 21 episodes of supraventricular and 39 episodes of ventricular arrhythmias,[94] disopyramide resulted in conversion to sinus rhythm in 3 of 8 patients with atrial flutter, 2 of 10 patients with atrial fibrillation, 1 of 3 patients with paroxysmal atrial tachycardia and 2 of 4 patients with sustained ventricular tachycardia. It suppressed nonsustained ventricular tachycardia in 9 of 12 patients, and reduced premature ventricular complexes by greater than 50 percent in 18 of 23 patients. Three patients had transient hypotension, requiring discontinuation of disopyramide in two. No patient experienced a new conduction defect or worsening of a preexistent defect.[94]

In a controlled double-blind trial,[96] the efficacy of disopyramide was compared with placebo in 95 patients (46 received disopyramide, 49 received placebo) after acute myocardial infarction. It was found that 21 patients treated with disopyramide and 42 patients treated with placebo required additional antiarrhythmic therapy to suppress various arrhythmias ($P < 0.0005$).

Four large multicenter studies[91] *provided important evidence of disopyramide's effectiveness in suppressing ventricular arrhythmias.* The first single blind study of 120 patients compared disopyramide (100 to 200 mg four times daily) with placebo, the second double blind study of 124 patients compared disopyramide (150 mg every 6 hours) with quinidine (325 mg every 6 hours), and the third study of 51 patients evaluated the acute efficiency of oral disopyramide (300 mg loading dose, 150 mg four times daily) compared with placebo, in suppressing arrhythmias. In the first study, disopyramide reduced the median number of premature ventricular complexes from approximately 170 to 35 per hour ($P < 0.01$). Thirty of 43 patients exhibiting ventricular tachycardia during placebo therapy had no episodes of ventricular tachycardia while receiving disopyramide. In the second study, there was no significant difference in efficacy between quinidine and disopyramide; however, adverse reactions were greater in patients treated with quinidine, and 22 of 62 patients

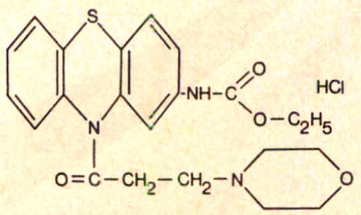


FIGURE 4. Chemical structure of ethmozin.

had to stop taking the drug, compared with 6 of 62 patients receiving disopyramide ($P < 0.01$). In the third study, 28 of 51 patients had greater than 50 percent reduction of premature atrial or ventricular complexes within 2 1/2 hours of the oral loading dose, and the suppression was maintained for 90 minutes. Six patients also experienced 50 percent reduction in ectopy but the subsequent 90 minutes were not available for analysis. Seventeen of 51 patients failed to meet these criteria and therapy was considered a failure. Twenty-seven of 48 patients who completed a full course of therapy had total abolition of ventricular tachycardia, couplets, R on T phenomenon, as well as a 75 percent or greater reduction in multiformity or frequency of premature ventricular complexes. Twelve of 48 patients had at least a 75 percent decrease in ventricular tachycardia and couplets plus at least a 50 percent decrease in multiformity or frequency of premature ventricular complexes and R on T events. The fourth study, begun in 1972, is a long-term evaluation of disopyramide in 468 patients. As of March 1976, approximately 50 percent of the patients in this study were no longer receiving disopyramide for a variety of reasons including death, side effects, medical problems unrelated to disopyramide and lack of effectiveness.[91]

Disopyramide has been successful in selected patients with drug-resistant ventricular tachycardia.[97,98] We have used it in five patients with ventricular tachycardia due to cardiomyopathy (four patients) and coronary artery disease (one patient) (unpublished observations). Conventional drugs and aprindine had failed to control the tachycardia in all five, tocainide had failed in four, and mexiletine had failed in two. Disopyramide successfully suppressed the ventricular tachycardia in two patients with cardiomyopathy, but failed in the other three.

Side effects: Ten to 40 percent of patients reported side effects due to anticholinergic activity of the drug, including dry mouth or urinary hesitancy. Three to 9 percent reported urinary retention, constipation, blurred vision and dry nose, eyes or throat. A similar percent complained of nausea or gastrointestinal distress.[91] Although the drug is like quinidine in many ways, disopyramide-induced "syncope" (that is, due to episodes of ventricular tachyarrhythmias)[99] or marked Q-T prolongation has not been reported at usual maintenance doses. One patient with a history of quinidine syncope manifested a prolonged Q-T interval and ventricular fibrillation while receiving 300 mg of disopyramide every 6 hours (personal communication, John J. Gallagher, MD).

Clinical pharmacology (Table I): Oral doses of disopyramide are 80 to 100 percent absorbed,[91,100] with oral bioavailability 60 percent of that of the intravenously administered drug.[91,101] Protein binding is concentration-dependent and ranges from 5 to 65 percent; at a serum concentration of 3 μg/ml, about 50 percent is protein-bound. The remainder of the drug presumably undergoes hepatic degradation with some of the metabolites excreted in the urine. At creatinine clearance levels of less than 40 ml/min, renal clearance of disopyramide is reduced. Change in urinary pH does not appear to significantly influence urinary excretion.[91] Disopyramide does not appear to be an enzyme-inducer.[91]

Hemodynamic studies of disopyramide (2 mg/kg intravenously over 3 minutes) in man revealed a mild decrease in cardiac output and increase in systemic vascular resistance.[89,90] The hemodynamic changes were generally small with doses less than 2 mg/kg intravenously.[94,102] In intact dogs, disopyramide decreased cardiac output, coronary blood flow and myocardial contractility.[86,103] Blood pressure was also reduced, systolic more than diastolic.[103,104]

Electrophysiology (Table II): Disopyramide exhibits electrophysiologic effects on isolated canine cardiac Purkinje fibers similar to the effects of procainamide and quinidine.[104–109] Disopyramide increased action potential duration and effective refractory period at concentrations of 1×10^{-6} molar, whereas at concentrations of 1×10^{-5} molar it reduced maximal diastolic potential, action potential amplitude, maximal upstroke velocity of phase 0, conduction velocity and spontaneous phase 4 depolarization; membrane responsiveness was reduced at concentrations of 1×10^{-5} molar or more. Increasing extracell potassium concentration potentiated, while decreasing extracell potassium concentration reduced the magnitude of the changes. Disopyramide had no effect on slow response action potentials and, in intact dogs, induced a concentration-dependent (1.1 to 24.6 μg/ml) prolongation of the P-R interval and QRS duration.[104–109]

In one study of patients given disopyramide (1 to 2 mg/kg intravenously over 5 to 10 minutes),[110] it had no significant effect on sinus nodal automaticity or on conduction through the A-V node (A-H interval) or His-Purkinje system (H-V interval). Disopyramide lengthened the relative refractory period of the His-Purkinje system, lengthened the effective refractory period of the atrium, and shortened the effective refractory period of the A-V node. Other studies have reported variable increases in P-R interval, QRS or Q-T duration.[86,87,103,104,110] When disopyramide (2 mg/kg per min intravenously over 2 minutes) was administered after atropine pretreatment (0.025 mg/kg), it prolonged the A-H interval and functional refractory period of the A-V node, prolonged the sinus nodal recovery time, slowed the heart rate and lengthened the effective refractory period of the atrium.[111] The results of this study suggest that some of the earlier observations of the electrophysiologic effects of disopyramide in man may have been influenced by changes in vagal tone brought about by disopyramide.

Ethmozin

Status: Ethmozin (Fig. 4) (Endo Laboratories, Inc.) is a phenothiazine derivative synthesized in the laboratory of Kaverina[112] at the Institute of Pharmacology of the USSR Academy of Medical Sciences in 1964. Clinical trials have been carried out in the Soviet Union[113] and investigational use of the drug clinically[114] has begun recently in the United States.

Clinical experience: Present information on the clinical efficacy of ethmozin in suppressing arrhythmias is based primarily on experience gathered within the Soviet Union. In the Soviet studies, the percent of patients in whom ethmozin reduced or eliminated the arrhythmia varied greatly, possibly because of different patient populations and doses.[113,115–117] However, a review of data collected from five clinics[113] revealed that ethmozin was most successful (in about 75 percent of patients) in treating paroxysmal atrial and ventricular tachycardia (55 patients) and atrial and ventricular premature complexes (123 patients) in patients with coronary artery disease or hypertension and after myocardial infarction. When ethmozin failed to terminate the tachycardia, it succeeded in reducing its rate. Ethmozin was less effective in patients with chronic atrial flutter, atrial fibrillation or sinus tachycardia. Oral doses generally used in these studies were 25 to 75 mg, given three times daily. Long-term electrocardiographic monitoring was not utilized in these Soviet studies.

In the United States, preliminary data have been obtained[114] from treating 12 patients with a variety of different cardiac problems, orally with 2.4 to 6.6 mg/kg per day for 7 pays, beginning and ending with 3 days of placebo therapy. Nine patients had exhibited resistance or intolerance to prior antiarrhythmic therapy. This study showed that ethmozin reduced the frequency of premature atrial complexes by a mean of 91 percent in four of five patients, but that reduction of premature ventricular complexes was dependent on dosage and plasma level, being maximum (78 percent reduction) in four patients who had received 5.5 mg/kg per day (mean) and had achieved a mean plasma concentration of 0.8 μg/ml. The only side effect was mild nausea in one patient. These studies suggest that the doses used in the initial Soviet studies may have been too small and that larger doses, apparently well tolerated, result in more beneficial responses.

Side effects: In the Soviet studies, the incidence of side effects ranged from 0 to 14 percent and included gastrointestinal problems such as nausea, vomiting and epigastric distress, neurologic side effects including vertigo, dizziness, dimmed vision and mild hypotension. The drug appears to be well tolerated, especially by elderly patients. In fact, in the American study[114] no significant side effects were observed despite doses three to five times as large as those used in the Soviet studies.

Clinical pharmacology (Table I): Relatively little has been published on the pharmacology of ethmozin in man. The drug was well absorbed from the stomach and small intestine in rats and was extensively metabolized (over 30 metabolites) in dogs and rats.[118]

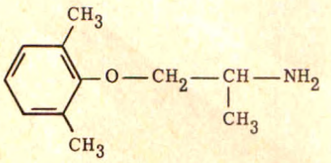


FIGURE 5. Chemical structure of mexiletine.

Electrophysiology (Table II): Danilo et al.[119] investigated the electrophysiologic effects of ethmozin on ventricular arrhythmias after a two-stage ligation of the left anterior descending coronary artery in conscious dogs. They found that ethmozin (1 to 3 mg/kg intravenously) reduced these arrhythmias for 15 to 30 minutes in three dogs, and at the same dose it also was effective against spontaneously occurring or epinephrine-induced ventricular arrhythmias that occurred 2 to 4 days after coronary occlusion in dogs. Orally administered ethmozin (10 to 20 mg/kg) was more effective in suppressing ventricular arrhythmias 24 hours after coronary occlusion than was quinidine (20 mg/kg orally).

These authors[119] also studied the effects of ethmozin on the transmembrane potentials of canine cardiac Purkinje fibers superfused with blood from a donor dog that had been given 1 to 3 mg/kg of ethmozin intravenously. One and 2 mg/kg had mild or no effects, whereas 3 mg/kg reduced maximal diastolic potential, action potential amplitude, rate of rise of the upstroke of phase 0 and action potential duration.

We[120] have evaluated the electrophysiologic properties of ethmozin and can confirm some of the previous observations. Ethmozin (1×10^{-6}, 1×10^{-5} g/ml) superfusion of Purkinje fibers decreased maximal rate of rise of phase zero, action potential amplitude and action potential duration and decreased the force of Purkinje fiber contraction. At a concentration of 1×10^{-7} g/ml, ethmozin increased the force of Purkinje fiber contraction. In intact dogs, ethmozin injected into the sinus or A-V nodal artery (1×10^{-6}, 1×10^{-5} g/ml) did not alter sinus discharge rate or A-V nodal conduction while 1×10^{-4} g/ml slowed the atrial rate. Given intravenously (3 to 5 mg/kg), ethmozin increased the excitability threshold, slightly increased ventricular muscle refractory period and increased the extent of ischemia-induced conduction delay during left anterior descending arterial occlusion. The latter effect probably accounted for the increased incidence of spontaneously occurring ventricular fibrillation, also produced by aprindine.[82]

Voltage clamp studies[121] on frog atrial muscle revealed that ethmozin reduced the fast sodium current due to a decrease in the maximal conductance of sodium ions and had no effect on the processes of activation, inactivation and reactivation of the sodium current.

Mexiletine

Status: Mexiletine (Fig. 5) (Mexitil®, Boehringer Ingelheim Ltd.) is a local anesthetic agent with anticonvulsant properties that was first used as an antiarrhythmic agent in 1969. Similar to lidocaine in many of

its actions, it was recently approved for clinical use in Europe and Great Britain, and investigational studies in patients have just begun in the United States.

Clinical experience: Several clinical trials have shown mexiletine to be an effective antiarrhythmic agent for treatment of both acute and chronic ventricular arrhythmias. In an early, uncontrolled study from Edinburgh,[122] mexiletine, given intravenously or orally, reduced the occurrence of premature ventricular complexes by more than 95 percent or eliminated ventricular tachycardia in 43 of 59 (72 percent) patients with ventricular arrhythmias due to a variety of causes, including myocardial infarction, cardiac surgery and digitalis toxicity. Some of the responders had arrhythmias that were not suppressed by lidocaine, procainamide, practolol or phenytoin given previously. Only four patients (7 percent) had no response to mexiletine. A similar report from Belfast confirmed these early observations.[123] In a prospective controlled study,[124] mexiletine (250 mg every 8 hours) was compared with procainamide (500 mg every 4 hours) in preventing ventricular arrhythmias in 60 men who had sustained acute myocardial infarction within the preceding 48 hours and also had required lidocaine for control of ventricular tachycardia or for premature ventricular complexes that fell in the T wave or were multiformed. Although only one third of patients receiving procainamide achieved accepted therapeutic blood concentrations, compared with 95 percent of patients receiving mexiletine, both drugs exhibited equal antiarrhythmic efficacy and patients in both drug groups had less serious ventricular arrhythmias than did the placebo-treated group ($P < 0.05$).

Several other noncontrolled studies[125,126] *have shown mexiletine to be effective,* given intravenously or orally, in suppressing ventricular arrhythmias in a variety of acute clinical situations, including acute myocardial infarction, after cardiac surgery and ventricular arrhythmias due to digitalis toxicity. In a double-blind protocol,[127] 97 patients hospitalized within 12 hours after symptoms of acute myocardial infarction were randomly assigned to treatment with mexiletine (600 mg initially, 200 mg at 2 and 4 hours, then 250 mg every 8 hours, orally) or to treatment with placebo. Ventricular fibrillation, ventricular tachycardia or R on T events occurred one or more times in the first 48 hours in 42 patients treated with placebo and in 18 patients treated with mexiletine. Three patients died, all in the mexiletine-treated group, because of cardiac rupture or cardiogenic shock. Two patients in the placebo-treated group had ventricular fibrillation. Thus, in this randomized controlled study,[127] mexiletine was shown to be an effective antiarrhythmic agent. Mexiletine has also been used successfully on a more chronic basis.[128–130]

Mexiletine (200 mg every 8 hours) was compared with sustained release procainamide (1.5 g every 8 hours), tolamolol (100 mg every 8 hours) and placebo in 20 patients with coronary artery disease who experienced more than 30 premature ventricular complexes per hour during a 24 hour period of ambulatory monitoring.[131] Each medication was administered in random order for successive 2 week periods, and each patient underwent 48 hours of ambulatory monitoring during the 2nd week. Mexiletine reduced the frequency of premature ventricular complexes by greater than 75 percent in 11 of 20 patients, whereas the frequency was reduced by procainamide in 12 of 20 patients and by tolamolol in 4 of 20 patients. Eight patients receiving procainamide had to reduce dosage because of side effects compared with only two patients receiving mexiletine and three taking tolamolol. In a continued longitudinal crossover study[132] of 25 patients with coronary artery disease complicated by symptomatic ventricular arrhythmias, the same authors found essentially the same results.

Our experience with mexiletine has been limited to chronic oral treatment (200 or 300 mg every 8 hours) of four patients with recurrent ventricular tachycardia due to coronary artery disease (three patients) or cardiomyopathy (unpublished observations). All patients had received conventional drugs, two had received aprindine and two had been treated with tocainide without suppression of their ventricular tachycardia. Mexiletine appeared to reduce the number of episodes of ventricular tachycardia in two of the three patients with coronary artery disease and in the one patient with cardiomyopathy, but the result was sufficiently successful to warrant continued therapy in only one patient with coronary artery disease. No patient experienced side effects.

Side effects: Most of the reported side effects occur during the initial administration of mexiletine and persist in a smaller percent of patients during maintenance treatment. Neurologic side effects include tremor, nystagmus, diplopia, dizziness, dysarthria, paresthesia, ataxia and confusion, and gastrointestinal disorders consist of nausea, vomiting and dyspepsia. Positive antinuclear factor and thrombocytopenia have been reported,[129] but do not appear to be common problems. Side effects appear more often with plasma mexiletine concentrations that exceed 1.5 to 2.0 μg/ml, although the overlap with therapeutic levels is great. Cardiac side effects include hypotension, bradycardia or exacerbation of arrhythmias. In spite of this list, the drug appears to be well tolerated.

Clinical pharmacology (Table I): Mexiletine was rapidly and well absorbed after oral ingestion in volunteers, but absorption was delayed and incomplete in patients with myocardial infarction and in patients receiving narcotic analgesic agents that retarded gastric emptying.[133] Therapeutic plasma concentrations of 1 to 2 μg/ml are maintained by oral doses of 200 to 300 mg every 6 to 8 hours, and the level of systemic availability of the orally administered drug is high. About 70 percent is protein-bound.[122]

Normally, mexiletine is eliminated metabolically by the liver, with less than 10 percent excreted unchanged in the urine. Renal clearance of mexiletine decreases as urinary pH increases.[133] The mean half-life is longer in patients treated in the coronary care unit than in normal volunteers.[133]

Mexiletine has only mild negative inotropic effects and it only slightly depressed contractility, similar to

the effects of lidocaine,[134–137] in several groups of patients with a variety of problems, including coronary artery disease[134] and aortic valve replacement.[135]

Electrophysiology (Table II): In man, mexiletine (200 to 250 mg intravenously over 5 minutes, followed by an infusion of 60 to 90 mg/hour) had no consistent effect on the frequency of sinus nodal discharge rate, sinoatrial conduction time or atrial refractoriness. It reduced the atrial rate at which Wenckebach block occurred, increased the functional refractory period of the A-V node, increased both the relative and effective refractory periods of the His-Purkinje system and prolonged the H-V interval.[138] When given at a dose of 3 mg/kg intravenously over 10 minutes to 20 patients with a variety of cardiac diseases, primarily coronary artery disease,[139] mexiletine shortened the relative refractory period of the His-Purkinje system and had no other consistent effects on sinus nodal function, A-V conduction intervals or refractory period of the atrium, A-V node or ventricle. The reasons for the difference in results between these two studies regarding the effects of mexiletine on relative refractory period of the His-Purkinje system is not known, but may reflect a difference between the two patient groups or differences in dosing regimens.

Mexiletine exhibits electrophysiologic properties similar to those of lidocaine[140–142] and has been effective in suppressing a variety of experimentally induced ventricular arrhythmias, including those that occurred 1 to 2 days after coronary arterial occlusion,[143] and those caused by digitalis intoxication[140,143] or adrenalin and halothane[143] administration.

Tocainide

Status: Tocainide (Fig. 6) (Astra Pharmaceutical), a primary amine analog of lidocaine, is now undergoing clinical trials in the United States. It differs from lidocaine in that it can be taken orally because it lacks two ethyl groups that contribute to lidocaine's first-pass hepatic degradation after oral administration.

Clinical experience: Most preliminary clinical evaluations of tocainide have been short-term studies in patients with stable, chronic premature ventricular complexes due to a variety of causes, including coronary artery disease and mitral valve prolapse. McDevitt et al.[144] treated patients who had premature ventricular complexes that averaged more than 60/hour and that could be suppressed by at least 50 percent with intravenous lidocaine (50 mg bolus dose, 25 mg every 10 minutes to a maximum of 125 mg in 30 minutes). Of seven patients, five experienced 63 to 98 percent reduction in the frequency of premature ventricular complexes over the 5 hour period after administration of 400 to 800 mg of a single oral dose of tocainide. Two patients who failed to respond had received 800 and 1,200 mg tocainide with plasma levels at 4 and 6.5 μg/ml. Effective plasma levels of the responders ranged from 1 to 5 μg/ml.

Winkle et al.[145] treated 15 patients who had chronic premature ventricular complexes in a single blind study, with placebo administered at the beginning and end of the protocol. Tocainide, given in doses of 400 and 600 mg orally, reduced premature ventricular complexes by more than 70 percent over an 8 hour interval at steady state in 11 of 15 patients. The average reduction was 91 percent with plasma concentration above 6 μg/ml. Mean tocainide concentrations were 6 and 8 μg/ml, respectively, for the two doses.

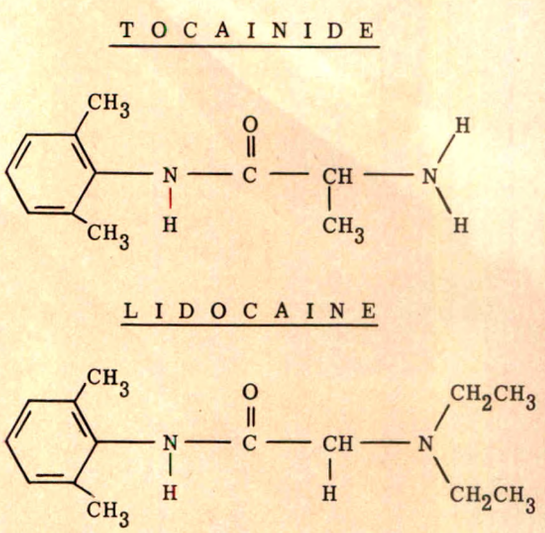


FIGURE 6. Chemical structure of tocainide and lidocaine.

Twelve patients who had stable premature ventricular complexes exceeding 500/12 hours underwent a dose-ranging study with tocainide.[146] Two patients discontinued the drug or reduced its dosage because of intolerable side effects without achieving suppression of arrhythmia, and two patients failed to achieve greater than 75 percent reduction in premature ventricular complexes at maximal allowable doses of tocainide. Thus, in eight patients, tocainide suppressed premature ventricular complexes from (mean ± standard error) 11.8 ± 4.3 to 2.08 ± 0.8/min (83.3 ± 4 percent suppression) for 8 to 12 hours at a dose of 688 ± 91 mg/12 hours. Those patients who experienced a reduction in premature ventricular complexes after administration of lidocaine also had a good response to tocainide.[146]

Very recent data[147] *have been obtained from 17 patients treated with tocainide* (800 to 2,100 mg daily; range of mean plasma concentrations, 6 to 12 μg/ml) for longer periods of time. Procainamide, quinidine and propranolol were either unsuccessful or not tolerated because of side effects. Nine patients had recurrent sustained ventricular tachycardia or ventricular fibrillation, three had nonsustained ventricular tachycardia that produced symptoms, and five patients had nonsustained ventricular tachycardia or premature ventricular complexes that did not produce symptoms. Success was judged by control of symptomatic episodes in the first group, control of major symptomatic occurrences and reduction in frequency of premature ventricular complexes in the second group, and sustained suppression of premature ventricular complexes in the third. Using these criteria, tocainide was successful in nine patients (53 percent). Of these nine patients, one had to discontinue the drug due to intol-

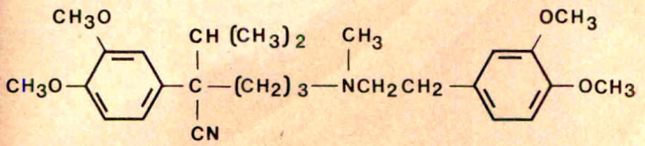


FIGURE 7. Chemical structure of verapamil.

erable side effects, another had a spontaneous decrease in "ventricular irritability" and has not been receiving tocainide, one has required a combination of quinidine and tocainide and another has needed a combination of tocainide and disopyramide. Two patients generally, but not always, had fewer premature ventricular complexes while receiving tocainide than during control periods.

We have treated five patients with recurrent ventricular tachycardia with tocainide (unpublished observations). All patients had failed to respond to conventional antiarrhythmic drugs plus a variety of other experimental antiarrhythmic agents. The patients included two female subjects, aged 2 and 32 years, and 1 man, aged 55 years, with cardiomyopathy, a 61 year old man with coronary artery disease and a 28 year old man with a probable cardiomyopathy. No patient appeared to have a significant reduction in the episodes of ventricular tachycardia while receiving 400 to 800 mg of tocainide every 8 hours (the child received 100 to 150 mg every 8 hours). They had no side effects.

Side effects: Gastrointestinal complaints are the most frequent side effects and include anorexia, nausea, vomiting, abdominal pain and constipation. Neurologic disturbances noted are tremor or twitching, headache, altered hearing, sweating, hot flashes, paresthesia, blurred vision or diplopia, nervousness, anxiety, dizziness or lightheadedness, and appear to be more related to dose than are the gastrointestinal side effects.[145,147] In spite of this relatively long list, the drug appears generally well tolerated, and a number of patients have taken it for many months.[147] The possibility that antinuclear antibody titers may become positive in some patients receiving tocainide has not been resolved completely.[148]

Clinical pharmacology (Table I): Tocainide appears to be rapidly and well absorbed, with peak serum levels occurring 60 to 90 minutes after drug administration. Therapeutic plasma concentrations of greater than 6 μg/ml result from oral doses of 400 to 600 mg every 8 hours. Bioavailability is high and the drug is 50 percent protein-bound. Renal excretion of unchanged drug averages 40 percent, and can be reduced to 20 percent of its original value by vigorous bicarbonate loading to maintain urinary pH above 7.4. Sixty percent of the drug presumably undergoes hepatic degradation.[149,150]

When infused intravenously at doses of 0.5 or 0.75 mg/kg per min for 15 minutes in 12 patients with compensated left ventricular dysfunction, tocainide produced small but statistically significant increases in pulmonary and systemic vascular resistance, aortic and pulmonary arterial pressures and left and right ventricular end-diastolic pressure. No significant change occurred in left ventricular dP/dt, heart rate or cardiac index. Plasma concentration at 15 minutes ranged between 7 (small dose group) and 11 (large dose group) μg/ml.[151]

Electrophysiology (Table II): In isolated superfused Purkinje fibers, tocainide decreased action potential duration at 50 percent repolarization (but not at 100 percent repolarization) and maximal rate of rise of phase 0 (dV/dt).[148] Effective refractory period tended to decrease. Results varied with different concentrations of the drug. For example, dV/dt increased at concentrations less than 15 μg/ml and the membrane responsiveness curve shifted to the left; however, concentrations exceeding 15 μg/ml decreased dV/dt and shifted the membrane responsiveness to the right.

The effects of tocainide on ischemia-related arrhythmias have been studied.[152] In large doses of 50 to 100 mg/kg (plasma levels 15 to 30 μg/ml), tocainide suppressed ventricular arrhythmias in unanesthetized dogs after coronary occlusion produced with ameroid constrictors. In this dose range, tocainide depressed mean aortic and left ventricular end-diastolic pressures and left ventricular dP/dt.

In dogs with ventricular arrhythmias 18 hours after coronary arterial ligation produced with a Harris two stage occlusion, tocainide reduced by 50 percent the mean frequency of ventricular ectopic beats when given in an oral cumulative dose of 75 mg/kg.[148] The antiarrhythmic effects appeared to be linearly related to plasma levels between 15 (threshold) and 30 (total suppression) μg/ml. Tocainide has also abolished ouabain-induced ventricular arrhythmias at an intravenous dose of 15 mg/kg in dogs.[148]

Tocainide (1 mg/kg per min) infused intravenously for 10 minutes before left anterior descending coronary artery ligation in open-chest anesthetized dogs resulted in 18 of 24 (75 percent) dogs developing ventricular fibrillation.[148] This percent was significantly higher than the development of ventricular fibrillation in the saline-treated controls (13 percent), or dogs treated with lidocaine (1 mg/kg per min, 15 percent), procainamide (1 mg/kg per min, 10 percent) or propranolol (0.02 mg/kg per min, 0 percent). A similar increase in the spontaneous development of ventricular fibrillation has been noted in dogs treated with aprindine[82] or ethmozin[120] given before coronary occlusion, and may relate to the negative dromotropic effects of these drugs.

Tocainide produced minimal electrophysiologic effects when infused (0.5 or 0.75 mg/kg per min for 15 minutes; peak plasma concentration 11.0 ± 1.7 μg/ml, mean ± standard error of the mean) into 11 patients.[153] The changes were qualitatively similar to those produced by lidocaine.

Verapamil

Status: Verapamil (Fig. 7) (Isoptin,® Iproveratril,® Cordilox®; Knoll Pharmaceutical), a papaverine derivative and slow-channel blocker, was first marketed in Germany in 1962 and investigated as an antianginal

drug in the United States shortly thereafter. However, clinical trials in the United States were stopped when early toxicologic studies in beagle dogs suggested that verapamil at large doses administered for a year may have caused cataracts. Subsequently, it was established that the lens protein of beagles differed from other species and that verapamil-induced cataracts appeared to be a species-specific occurrence. No lens changes or eye problems definitely attributable to verapamil have occurred in other animals or during 15 years of worldwide clinical experience. Therefore, very recently, clinical investigation of verapamil in the United States has been renewed and the drug is now being used orally and intravenously at several centers.[154] It is available clinically throughout much of the rest of the world.

Clinical experience: Verapamil gained initial clinical use as a coronary vasodilator[155] in the treatment of ischemic heart disease.[156] In a double-blind evaluation[157] of verapamil, propranolol and isosorbide dinitrate against placebo, verapamil (120 mg three times daily) and propranolol (100 mg three times daily) had equal efficacy in the treatment of angina of effort, and both preparations were more effective than isosorbide dinitrate and placebo. A double blind crossover study[158] of verapamil (80 mg three times daily), practolol (100 mg three times daily) and placebo in patients with angina pectoris established verapamil as the most effective in treating angina.

Some recent studies indicate that verapamil given before (0.8 to 3.5 mg/kg)[159] or 15 minutes after (0.2 mg/kg)[160] coronary occlusion reduces the extent of myocardial necrosis. Verapamil (0.2 mg/kg intravenously) given before coronary occlusion reduced ischemia-induced conduction delay as well as the frequency of ventricular arrhythmias[161] in dogs. When given intravenously to dogs beginning 5 hours after the initial plasma creatine kinase elevation that followed coronary artery occlusion, verapamil (0.2 to 0.7 mg/kg/hr) increased blood flow in normal but not in ischemic myocardium and did not limit the extent of infarction.[162] A study[163] in 14 patients with acute myocardial infarction concluded, based on predicted infarct size using serum creatine kinase analysis and S-T segment mapping, that administration of verapamil resulted in diminished infarct size in selected patients. Verapamil has also been noted to exert mild antihypertensive effects.[157] However, development of its major clinical application to date has been for the treatment of cardiac arrhythmias.[164]

Intravenously administered verapamil has been shown repeatedly to be extremely effective in terminating episodes of paroxysmal suppraventricular tachycardia,[165–167] in patients with[168–170] and without the Wolff-Parkinson-White syndrome,[171] and in slowing the ventricular rate and also restoring sinus rhythm in patients with atrial flutter[172] and atrial fibrillation.[165,167,173] In one large study,[165] verapamil (10 mg intravenously over 15 to 30 seconds) slowed the ventricular response in 111 of 115 patients with atrial fibrillation, restored sinus rhythm in 4 of 15 patients with atrial flutter, slowing the ventricular rate in the other 11, and converted all 20 episodes of paroxysmal supraventricular tachycardia to sinus rhythm. Subsequent reports have confirmed these early observations.[168]

In a study of 44 patients with supraventricular and ventricular tachyarrhythmias, intravenously administered verapamil promptly restored sinus rhythm in 13 of 17 patients with paroxysmal supraventricular tachycardia but in only 2 of 11 patients with atrial flutter and in 1 of 12 patients with atrial fibrillation. Slowing of the ventricular rate was transient in those patients who did not have conversion to sinus rhythm, suggesting that the drug, given intravenously, had limited usefulness for patients with atrial flutter and atrial fibrillation,[174] unless an initial bolus injection was followed by an infusion or oral maintenance. Verapamil terminated ventricular tachycardia in only one of five patients in this study.

A review[154] of 134 clinical papers published throughout the world revealed that intravenously administered verapamil (5 or 10 mg) converted to sinus rhythm 80 percent of episodes of supraventricular tachycardia, 30 percent of episodes of atrial flutter and 16 percent of episodes of atrial fibrillation. In those patients who did not have conversion to sinus rhythm, verapamil slowed the ventricular rate in 9 percent of those with supraventricular tachycardia, 54 percent of those with atrial flutter and 78 percent of those with atrial fibrillation. Thus, the effectiveness of intravenously administered verapamil in restoring sinus rhythm, especially in patients with supraventricular tachycardia, or in slowing the ventricular rate in patients with atrial flutter or atrial fibrillation, appears quite convincing.

The effectiveness of orally administered verapamil in treating arrhythmias has been less well documented than the efficacy of the drug given intravenously. However, a number of reports[175–177] indicate successful slowing of the ventricular rate or restoration of sinus rhythm in episodes of atrial flutter, atrial fibrillation or supraventricular tachycardia. A review[154] of seven studies in which 90 episodes of supraventricular tachycardia were treated with oral verapamil reveal that sinus rhythm was restored in 28 (31 percent) and the ventricular rate reduced in 46 (51 percent). In three studies reporting a total of 16 episodes of atrial flutter, oral verapamil converted 2 episodes (13 percent) to sinus rhythm and slowed the ventricular rate in 13 (81 percent). In 11 studies of 113 episodes of atrial fibrillation, oral verapamil converted 6 episodes (5 percent) to sinus rhythm and slowed the ventricular rate in 83 (74 percent). The prophylactic use of verapamil in preventing recurrences of supraventricular tachyarrhythmias needs further documentation. An initial report is encouraging.[178]

Verapamil has been less effective in treating patients with ventricular arrhythmias, but it has been found useful in a number of instances. A review of 31 studies[154] in which 239 episodes of ventricular tachyarrhythmias were treated with verapamil revealed that verapamil restored sinus rhythm in two thirds of the episodes. In a recent study[179] of four patients with

chronic recurrent sustained ventricular tachycardia, verapamil was ineffective in all four.

We[180] have treated with verapamil (5 to 10 mg intravenously) seven episodes of paroxysmal supraventricular tachycardia in four patients. In all but one episode there was conversion to sinus rhythm (mean conversion time 2.5 minutes after beginning administration of verapamil). The failure occurred in a patient with an accessory pathway conducting in retrograde fashion Pi (concealed Wolff-Parkinson-White syndrome)[17,181] in whom verapamil slowed the rate of paroxysmal supraventricular tachycardia from 180 to 162/min but failed to terminate it. Two episodes of atrial fibrillation in one patient and one episode of atrial flutter in each of two patients were similarly treated, with reduction of the ventricular rate from 175 to 115/min (mean). Sinus rhythm returned (mean conversion time 3 hours, 4 minutes) in all patients. We also have treated with oral verapamil three patients with recurrent paroxysmal supraventricular tachycardia, but the follow-up period is too short to permit comment.

Side effects: An analysis of data from more than 8,000 patients treated with verapamil reveals the drug to be very well tolerated.[154] The reported incidence of adverse reactions was 9 percent with only 1 percent of patients requiring discontinuation of the drug because of side effects. Cardiovascular adverse effects (3.7 percent) included bradycardia, transient asystole, hypotension, development of or worsening of heart failure, or development of rhythm disturbances.[182–186] Central nervous system problems (2.2 percent) were primarily headache and dizziness, and gastrointestinal disturbances (2.2 percent) usually included constipation and nausea. A variety of miscellaneous side effects (0.8 percent) were noted, such as skin reactions and dyspnea. The drug should be avoided or used with caution in patients with sick sinus syndrome, atrioventricular conduction disturbances or severe congestive heart failure, and is contraindicated in combination with beta adrenergic receptor blocking agents.

Clinical pharmacology (Table I): Verapamil appears to be rapidly and nearly completely (90 percent) absorbed after oral administration in humans.[187,188] On the basis of observations that only a low concentration of unchanged drug can be measured in plasma and only negligible amounts are excreted unchanged, the drug must be highly metabolized, with metabolites excreted in the urine and in the bile. Metabolite concentration gradually rises with continued administration of the drug, but the metabolites appear only weakly active. Extensive metabolism occurs in the liver, as N or O-demethylation, or both.[189] Approximately 20 to 30 percent of verapamil is protein-bound.[190] Bioavailability of the oral dose is only 10 to 20 percent of the intravenous dose, because of hepatic metabolism, and it is estimated that the effective oral dose must be 8 to 10 times the amount of the intravenous dose.[154]

The effects of verapamil on A-V nodal conduction, as an indication of verapamil's bioactivity, were compared with plasma concentration. Verapamil (240 mg orally) was found to act 2 hours after ingestion, with peak effects at 5 hours,[191] which does not coincide with peak concentrations of total activity or of unchanged drug in plasma, measured with ^{14}C-labeled verapamil to be between 30 and 45 minutes.[192] However, when verapamil was given to dogs intravenously (3.0 mg/min for 10 minutes or 1.5 mg/min until the development of second degree A-V block), the correlation between plasma concentration and P-R interval was excellent.[193]

Surprisingly, in view of the calcium-blocking properties of verapamil, its hemodynamic effects in man have been relatively slight, and can be ascribed to a mild negative inotropic effect.[154] Most hemodynamic studies suggest that clinical doses of verapamil cause peripheral vasodilation, leading to a sympathetic reflex that opposes the direct effects of verapamil to decrease contractility or sinus rate.[194,195] The net effect on heart rate or on contractility depends on several factors, including the prevailing level of autonomic tone and the contractile state of the myocardium. Several studies in man and animals support this conclusion.

In 14 patients with acute myocardial infarction,[163] verapamil (7.5 mg bolus dose followed by 0.1 mg/min infusion over 10 hours) reduced mean aterial pressure from 98.2 to 85.1 mm Hg and left ventricular stroke work from 43.3 to 33.8 g-m/m^2, whereas the filling pressure of 13 mm Hg did not change significantly. In a group of seven healthy subjects,[196] verapamil (7.5 to 12 mg intravenously) caused an increase in heart rate and cardiac output with a concomitant decrease in blood pressure and peripheral resistance. Negative inotropic effects were not observed, probably because they were masked by reflex sympathetic stimulation in response to the decreased blood pressure and peripheral resistance.

Six patients subjected to diagnostic cardiac catheterization[197] were given verapamil (10 mg intravenous bolus dose) and noted to have an initial transient (18 percent) decrease in left ventricular systolic pressure and decreases in peak left ventricular dP/dt and Vmax and an increase in left ventricular end-diastolic pressure. Heart rate increased but cardiac and stroke index did not change. In 13 patients with coronary artery disease and seven patients with cardiac valve disease of rheumatic origin,[198] verapamil (10 mg intravenously) reduced arterial blood pressure and systemic vascular resistance, increased left ventricular end-diastolic pressure and reduced left ventricular dP/dt max. Changes in heart rate, cardiac index, left ventricular minute work and mean pulmonary arterial pressure were not significant. Verapamil has also been reported to increase coronary blood flow in patients without, but not with, coronary artery disease.[199]

In dogs,[200] verapamil (0.2 mg/kg bolus dose, followed by 0.2 mg/kg infusion) reduced coronary vascular and peripheral resistance, increased myocardial blood flow, heart rate and cardiac output. After beta adrenergic receptor blockade, verapamil caused little change in heart rate or output, but the increase in coronary blood flow and decrease in coronary vascular resistance still occurred. A similar study[195] obtained from conscious

dogs given verapamil intravenously (0.125, 0.25, 0.3.75 mg/kg) demonstrated vasodilating and negative inotropic effects, with increased heart rate, decreased stroke volume, decreased mean aortic pressure, decreased total peripheral resistance and decreased dP/dt max. Verapamil given after pretreatment with propranolol plus atropine produced a bradycardia, thus supporting the conclusion that verapamil exerts opposing direct and indirect effects on heart rate and contractility.

The mechanism of action of verapamil is to block the transmembrane influx of calcium (and possibly sodium, under some circumstances)[201] through what has been called the slow channel, without affecting to any significant degree transmembrane influx of sodium through the fast channel.[202–204] Verapamil does not modify calcium-binding or release by isolated sarcoplasmic reticulum fragments,[205,206] has no effect on calcium-activated adenosine triphosphatase[205,207] and does not diminish catecholamine-induced increases in tissue levels of cyclic adenosine monophosphate.[206] Verapamil also does not block the ability of epinephrine to activate myocardial adenylate cyclase,[206] and is clearly not a beta adrenergic receptor antagonist. The optical isomers of verapamil may exert different effects with (−) verapamil more potently and primarily blocking the slow channel and (+) verapamil exhibiting some fast-channel inhibiting properties.[208,209]

Verapamil depresses myocardial contractility,[205,210] an event accompanied by a decrease in the myocardial demand for oxygen. Contractility in the ischemic myocardium appears to be selectively depressed,[211] which may explain the reduction in ischemic injury produced with verapamil.[159]

Electrophysiology (Table II): Verapamil, by blocking the slow channel, exhibits electrophysiologic effects different from those of other antiarrhythmic agents.[212] In isolated tissues,[213] at low to moderate concentrations, verapamil exerts little or no effect on action potential amplitude or maximal rate of rise of phase 0 in cells with fast response characteristics (atrial and ventricular muscle, His-Purkinje system) but suppresses activity in the sinus and A-V nodes and in abnormally depressed fibers with slow-channel dependent properties. At concentrations less than 2×10^{-6} molar, verapamil had no effect on canine Purkinje fibers[214]; at 2×10^{-6} molar it enhanced phase 1 and increased the slope of phase 2 repolarization, whereas at concentrations greater than 6×10^{-5} molar it had more pronounced effect on repolarization and decreased action potential amplitude, resting membrane potential, maximal rate of rise of phase 0, membrane responsiveness and conduction velocity. Verapamil 2×10^{-6} molar suppressed automaticity in normal Purkinje fibers and those exposed to ouabain.

Verapamil, at concentrations that do not affect ordinary fast responses, may suppress electrical activity from diseased atrial[215] *or ventricular*[216] *muscle fibers that have reduced resting potentials,* suggesting that these cells depend on transmembrane calcium (or sodium) flux through the slow channel. Similarly, verapamil suppresses slow responses elicited by a variety of methods.[217,218] Verapamil also suppressed triggered sustained rhythmic activity in the simian mitral valve,[219] the canine coronary sinus[220] or induced by ouabain[221,222] or acetylstrophanthidin[223] in Purkinje fibers.

When given intravenously (0.2 mg/kg) to dogs before a 5 minute occlusion of the left anterior descending coronary artery,[161] verapamil reduced the extent of ischemia-induced conduction delay and the incidence of ventricular fibrillation from three of eight to zero of eight dogs. When given intravenously (0.25 mg/kg) to dogs after a 15 minute coronary occlusion,[224] verapamil slowed conduction in the ischemic zone and did not reduce the incidence of ventricular extrasystoles. Methodologic differences between these two studies account for the contradictory results.

Activity within the sinus and A-V nodes seems to be particularly sensitive to the suppressant effects of verapamil,[225,226] because normal impulse formation in the sinus node and conduction in the A-V node appear to be maintained by operation of slow channel-dependent mechanisms.[213,227–230] Verapamil suppresses electrical activity in sinus and A-V nodal cells at concentrations that do not significantly affect neighboring atrial muscle or the His-Purkinje system. The depressant effect exerted by verapamil on spontaneous sinus nodal discharge and A-V nodal conduction may in part explain its effectiveness in treating supraventricular tachyarrhythmias.

In man, consistent with the experimental observations of the effects of verapamil on sinus and A-V nodal activity, verapamil (10 mg intravenously) prolonged conduction time through the A-V node (A-H interval), without affecting the P-A, H-V or QRS intervals[168,231–233] and lengthened the functional and effective refractory periods of the A-V node.[171] Spontaneous sinus rate may slow, an event only partially reversed by atropine.[234]

Conclusions

These seven antiarrhythmic agents, plus several new beta adrenergic receptor blocking drugs, bretylium and other compounds still in early testing stages, represent promising advances for the therapy of cardiac arrhythmias. Although pacing and surgical ablation techniques have resulted in spectacular successes for some patients with certain types of drug-resistant tachyarrhythmias, the vast majority of patients must be treated medically because of the large number with symptomatic and even life-threatening cardiac arrhythmias. If the tachyarrhythmia does not respond to procainamide, quinidine, propranolol or diphenylhydantoin, or if the patient cannot tolerate these agents, other antiarrhythmic drugs must be available to the practicing cardiologist. As more effective antiarrhythmic agents with fewer side effects are developed, the need for pacing and surgical approaches will diminish.

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Electrical Management of Arrhythmias With Emphasis on The Tachycardias

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Information from stimulation studies in human beings with tachycardia has resulted in the application of cardiac pacing in the treatment of such patients. Short-term pacing is especially useful in patients with atrial flutter. Long-term pacing with use of chronically implanted units can be applied to patients with different types of supraventricular and ventricular tachycardia. In these patients careful electrophysiologic studies are required before the pacing device is implanted. New developments enabling automatic and more individually designed modes of pacing are urgently needed.

High energy shocks for life-threatening arrhythmias and pacemaker therapy for symptomatic bradycardia are examples of the use of electricity in the management of cardiac arrhythmias. Both techniques have become indispensable in daily care of the cardiac patient. Recently it was demonstrated that cardiac pacing can also be helpful in the prevention and treatment of tachycardias.[1–4] In this article we review the use of cardiac pacing in the short- and long-term management of patients suffering from tachycardias.

Electrophysiologic Mechanisms of Tachycardia Control by Pacing

In discussing the value of pacing in patients with tachycardia it seems appropriate to start by reviewing possible ways in which pacing interferes with arrhythmogenic mechanisms. Abnormal automaticity and reentry, alone or in combination, are accepted mechanisms for the genesis of arrhythmias. Initiation of tachycardia by any of these mechanisms is influenced by many factors including basic heart rate, premature beats and structural and functional properties of the cardiac tissue. Frequently, these factors are closely interrelated.

Role of Pacing In Prevention of Tachycardias

Basic heart rate: Abnormal automaticity is favored by slow heart rates and, under certain circumstances, such as digitalis intoxication,[5,6] also by fast heart rates. The occurrence of reentry is facilitated by both slow and fast heart rates.[7]

Patients with a slow heart rate due either to the "sick sinus syndrome" or to high degree atrioventricular (A-V) block frequently suffer from supraventricular or ventricular tachyarrhythmias or both, as in the so-called bradycardia-tachycardia syndrome.[8] In some of these patients the occurrence of the arrhythmia can be suppressed or prevented simply by increasing heart rate by pacing.[9] An example is given in Figure 1. The higher heart rate not only has a stabilizing effect on the arrhythmogenic mechanisms, but also enables the use of antiarrhythmic drugs without fear of further depression of heart rate.

Although increasing heart rate may result in control of arrhythmias, it has correctly been stressed that especially in patients with significant cardiac decompensation ventricular pacing might lead to hemodynamic

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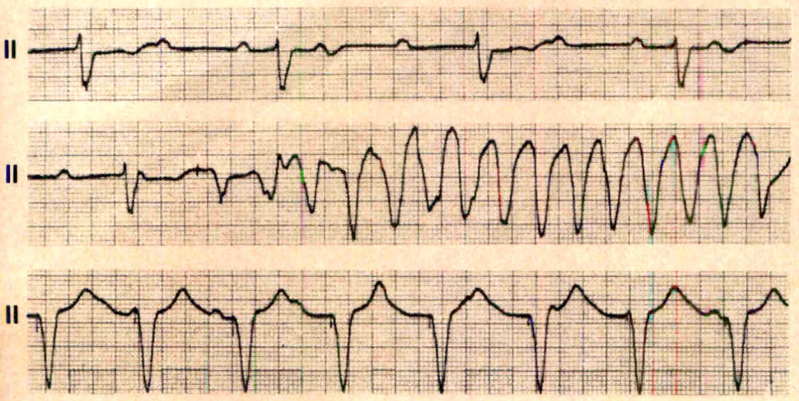


FIGURE 1. Rhythm strips, lead II. Ventricular tachycardia **(middle strip)** in a patient with complete atrioventricular block (ventricular rate 35/min, **upper strip**) is controlled with ventricular pacing at a rate of 70/min **(lower strip).**

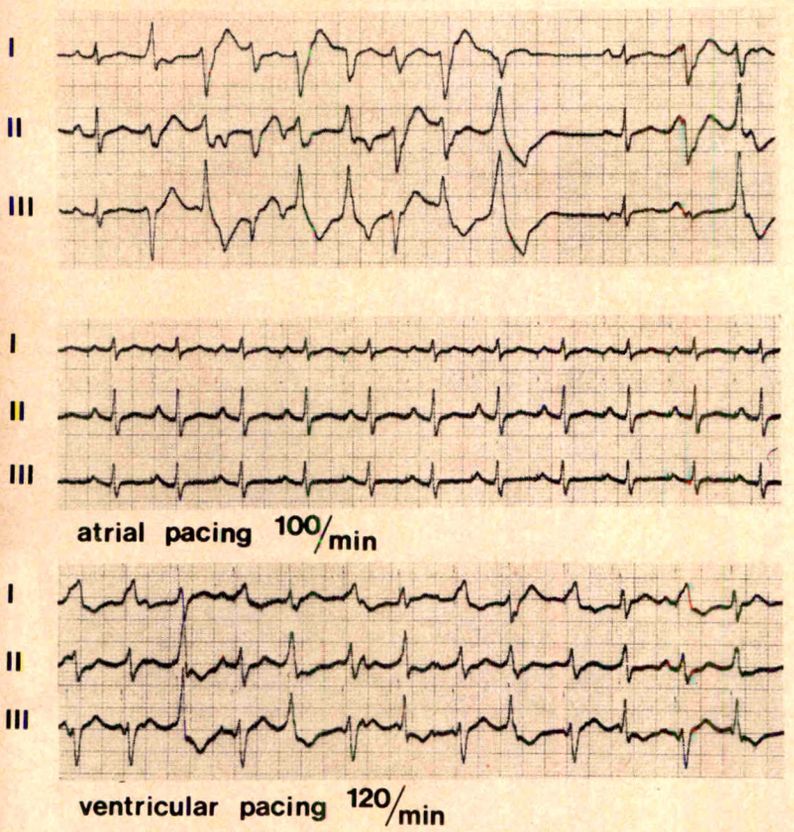


FIGURE 2. Electrocardiograms (leads, I, II and III) showing importance of spread of ventricular activation in control of ventricular arrhythmias with pacing. The patient was a 35 year old woman with multiform ventricular ectopic activity that could not be controlled with drug therapy **(upper tracing).** Atrial pacing at a rate of 100/min completely prevented ectopic activity **(middle tracing).** However, ventricular pacing at rates above 100/min (**lower tracing,** 120/min) did not control the arrhythmia.

deterioration because of loss of atrial contribution to cardiac output.[10] It is advisable, therefore, prior to implanting a pacemaker in patients in whom supraventricular or ventricular arrhythmias are shown to be facilitated by slow supraventricular rhythms or high degree A-V block, to determine the effect of the pacing mode on cardiac output. In such patients, one will often find it preferable to implant a pacemaker device that preserves atrial contribution to ventricular filling. Selection of the type of pacemaker (atrial demand, synchronized or sequential A-V or bifocal) will depend on the properties and size of the atrium and the electrophysiologic properties of the A-V conduction system.[10]

Spread of activation during pacing: Suppression of arrhythmias by increasing heart rate with pacing depends not only on reaching a critical heart rate but sometimes also on the pattern of cardiac activation after the paced impulse. In the patient whose tracings are shown in Figure 2, multiform ventricular ectopic activity could be controlled by pacing the right atrium at a rate of 100/min, but not by ventricular pacing at similar or higher heart rates. We have also observed the opposite: In some patients control of ventricular arrhythmias could be accomplished by ventricular pacing at lower heart rates than during atrial pacing. These observations suggest that sequence of activation may play a role in the genesis of arrhythmias.

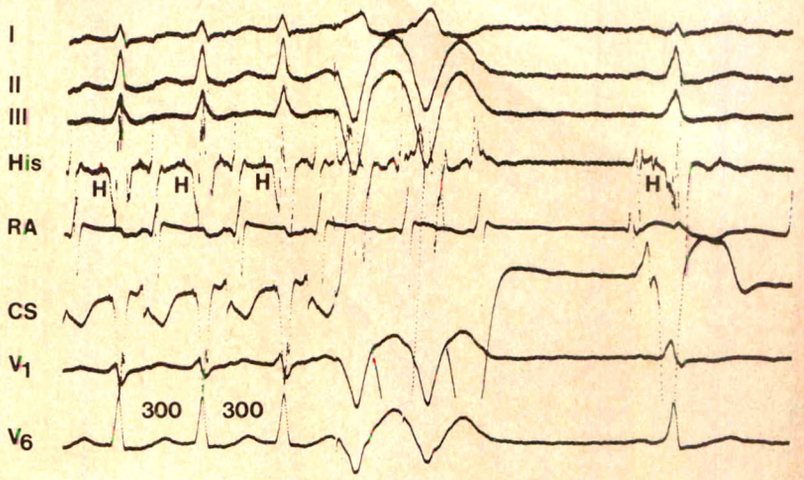


FIGURE 3. Recordings showing importance of site of stimulation in termination of tachycardia. In this patient with the Wolff-Parkinson-White syndrome, type A, two right ventricular premature complexes were needed to terminate tachycardia. **From top to bottom:** leads I, II, III, His bundle recording (His), high right atrial lead (RA), coronary sinus lead (CS) and leads V_1 and V_6 recorded simultaneously. H = His deflection; numbers indicate pacing cycle length (msec).

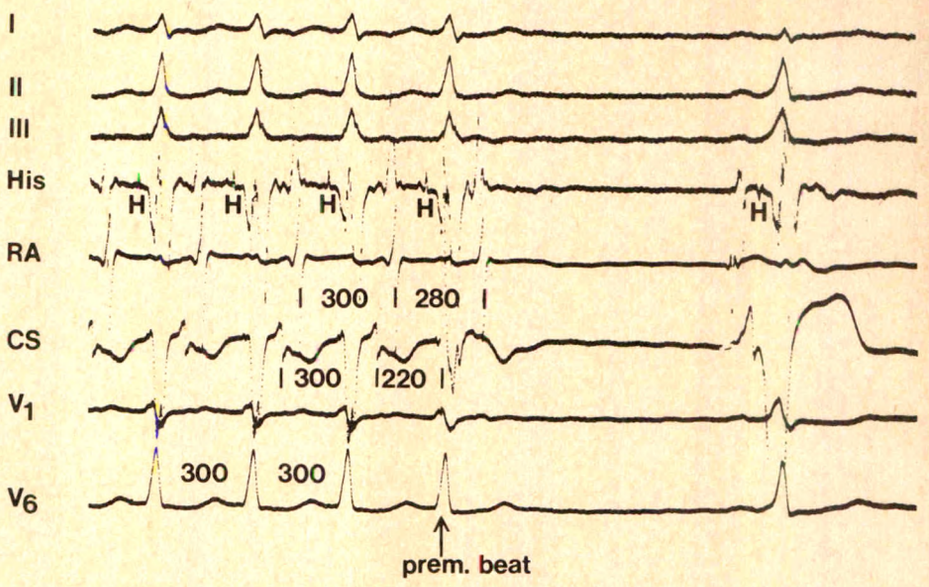


FIGURE 4. Recordings showing importance of site of stimulation in termination of tachycardia. Same patient as in Figure 3. When timed stimuli are given from the coronary sinus (CS), because of greater proximity to the tachycardia circuit, only a single premature (prem.) beat is required to terminate the tachycardia. Abbreviations as in Figure 3.

Termination of Tachycardia With Timed Stimuli

Timed stimuli: Termination of tachycardia with use of appropriately timed stimuli has been demonstrated in patients with tachycardias thought to be due to a reentry mechanism. As discussed elsewhere,[11] this is true for patients with different types of supraventricular and ventricular tachycardias.[12–18] The given explanation for this phenomenon is invasion of the reentry circuit by the electrically induced impulse, thereby creating refractoriness ahead of the circulating impulse responsible for the tachycardia. Although definite experimental evidence is not available, from clinical observations we assume that block in the reentry circuit after the induced impulse occurs in the weak link of the circuit, the latter being defined as the part of the circuit with the longest functional refractory period. This weak link in the circuit may vary from patient to patient. In those with the Wolff-Parkinson-White syndrome it can be either the A-V node or the accessory pathway; in those with A-V nodal reentry tachycardia it is usually the anterograde A-V nodal pathway.

Several factors affect the ability to terminate reentry tachycardias with timed stimuli. As recently reviewed,[11] they include: (1) the size and site of the tachycardia circuit; (2) the distance between the site of stimulation and the site of tachycardia circuit; (3) the heart rate during tachycardia; and (4) the electrophysiologic properties of the tissue or tissues between the site of stimulation and the tachycardia circuit. A typical example of the importance of the site of stimulation in terminating tachycardia is given in Figures 3 and 4. In this patient suffering from the Wolff-Parkinson-White syndrome, during tachycardia with a rate of 200/min, two right ventricular premature complexes were required to terminate tachycardia. From the coronary sinus, which was located close to the left-sided accessory pathway part of the reentry circuit, only one premature complex was needed. We and others[19,20] have

also stressed the importance of the site of stimulation in terminating ventricular tachycardia with timed stimuli. This is illustrated in Figure 5.

Especially during faster heart rates, the site and size of the reentry circuit and the distance between the circuit and the stimulation site become important factors in determining the number of premature complexes required to terminate tachycardia. For example, we found that in all 35 of our patients with A-V nodal reentry tachycardia and a heart rate of more than 160 beats/min, two or more ventricular premature complexes were required to terminate tachycardia. However, in

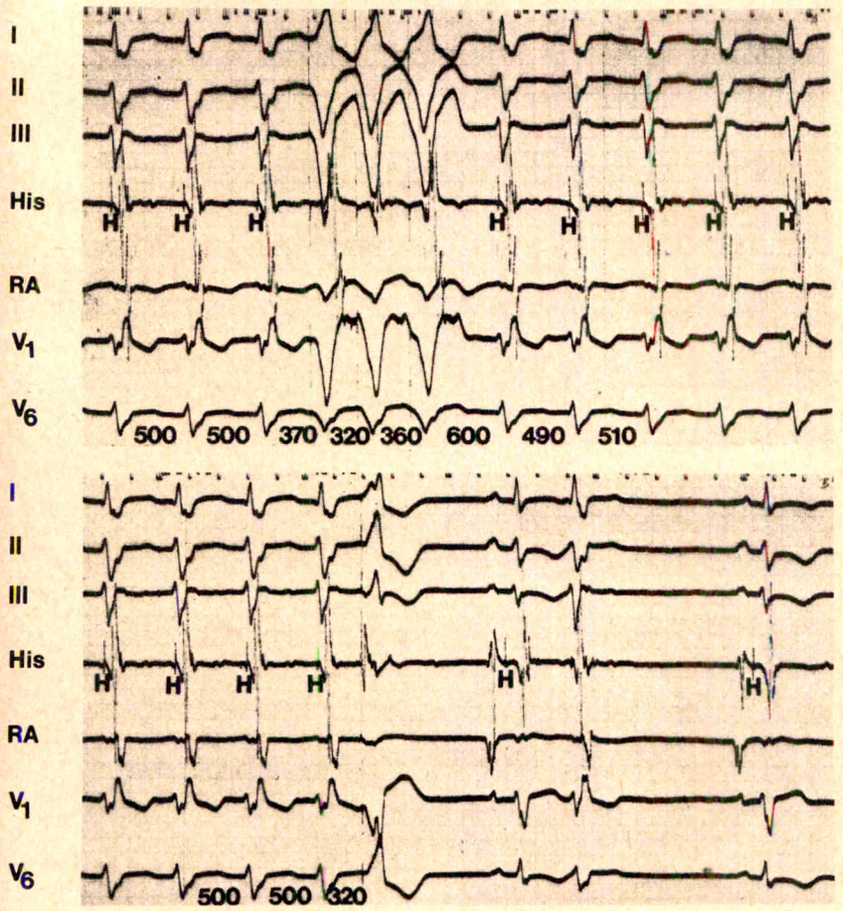


FIGURE 5. Recordings showing importance of site of stimulation in terminating ventricular tachycardia. In the **upper tracing,** three consecutively given ventricular premature complexes from the apex of the right ventricle fail to terminate tachycardia. In the **lower tracing,** only a single premature complex, given in the outflow tract of the right ventricle, terminates the tachycardia. In this patient activation of the bundle of His (H) during tachycardia occurs 30 msec after the onset of the QRS complex. Abbreviations as in Figure 3.

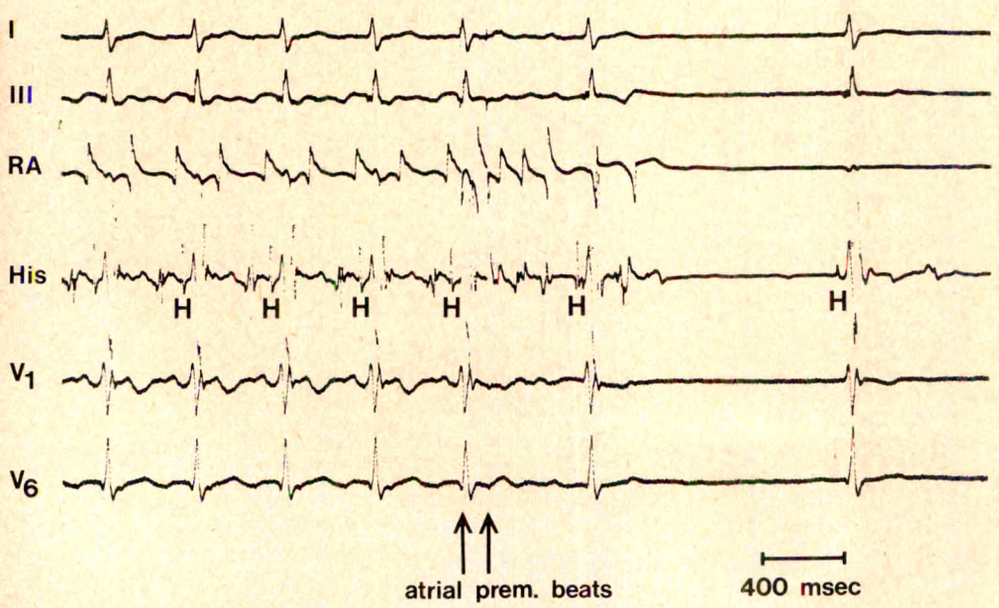


FIGURE 6. Recordings showing termination of atrial flutter by two closely given atrial premature (prem.) stimuli. In the right atrial lead (RA) a brief episode of atrial fibrillation precedes atrial arrest. Arrest is terminated by an A-V junctional escape beat. Abbreviations as in Figure 3.

patients with a reentry tachycardia incorporating an accessory A-V connection and a similarly high heart rate, tachycardia could be terminated with a single ventricular premature complex in 28 of 64 patients.[21] Especially in the situation of a small tachycardia circuit and a high heart rate during tachycardia, termination of tachycardia with timed stimuli can be extremely difficult. This is probably why atrial flutter usually cannot be terminated by one or two premature atrial stimuli, but requires pacing at rates above the flutter frequency.[22–26] In our experience and that of others,[22,24–26] frequently a period of unstable atrial fibrillation precedes termination of atrial flutter. Only occasionally atrial flutter can be terminated by a single atrial premature stimulus[14] or by two closely given atrial premature stimuli. However, as shown in Figure 6, usually a short period of atrial fibrillation occurs before reversion to sinus rhythm.

"Overdrive" pacing: In patients with tachycardia the arrhythmia can frequently be terminated by driving at rates above the tachycardia frequency. This method of pacing is called "overdrive" pacing. It can be successful when single or double stimuli fail to interrupt the tachycardia. We assume that abbreviation of the refractory period at the site of stimulation because of the faster pacing rate, enables shorter coupling intervals for the pacing-induced depolarizations, thus allowing impulses to arrive earlier at the site of the reentry circuit, facilitating invasion into this area. "Overdrive" pacing in patients with abnormal automaticity may result in temporary slowing or cessation of tachycardia but not in long-lasting termination (Fig. 7). Occasionally one may observe that "overdrive" pacing fails to terminate tachycardia, whereas a critically timed premature stimulus is able to do so (Fig. 8).

Clinical Applications

Short-Term Pacing

Atrial flutter: Atrial flutter has become the type of tachycardia most suitable for treatment with temporary pacing. The ventricular rate during atrial flutter is frequently difficult to control with drugs that have a small margin between therapeutic and toxic effects. This holds for atrial flutter not only after cardiac surgery,[23] but also when the arrhythmia occurs consequent to myocardial infarction or pulmonary disease.[27] Often drug treatment is not successful in controlling ventricular rate and the digitalis given increases the danger of induction of ventricular fibrillation during cardioversion.

In our experience stimulation can be most successfully performed low in the atrium, using gradually increasing pacing rates and stimulus strength. Because under these circumstances stimulation is performed close to the ventricle, the atrial position of the stimulating catheter should be carefully checked with fluoroscopy and electrographic recording from the stimulating electrodes. Using these principles we were able to terminate the arrhythmia in 36 of 40 consecutive

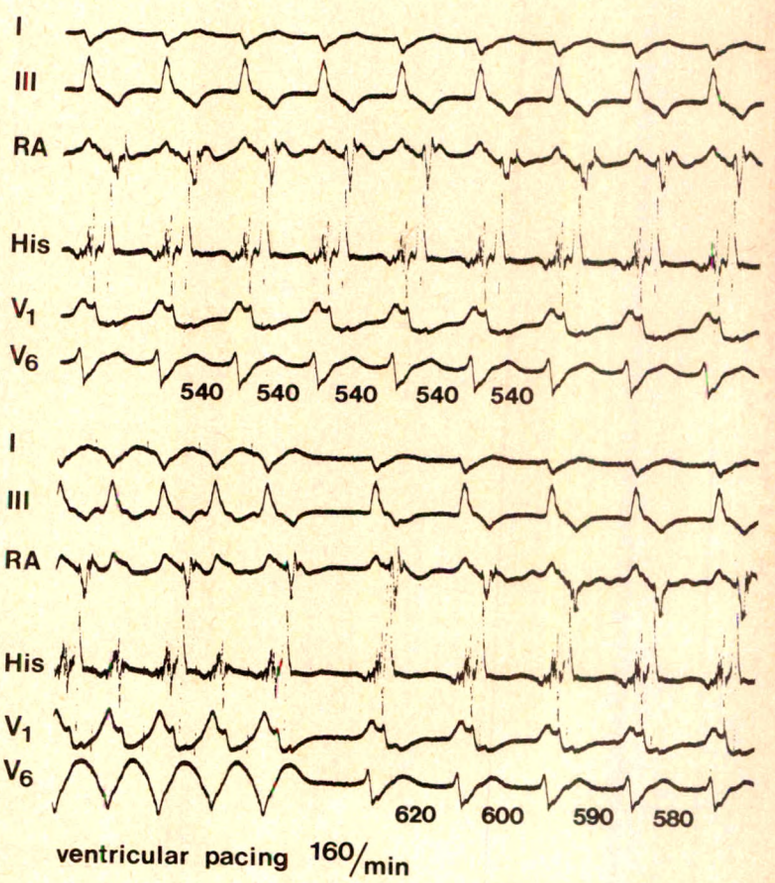


FIGURE 7. Top panel, recordings showing ventricular tachycardia before "overdrive" pacing. Note the R-R interval of 540 msec. **Lower panel,** after termination of left ventricular "overdrive" pacing, ventricular tachycardia emerges at a slower rate than before pacing. Ten complexes of ventricular tachycardia were required to reach the pre-"overdrive" R-R interval of 540 msec (not shown). The tachycardia could not be terminated by "overdrive" pacing or single, double or triple premature stimuli from several sites in the left and right ventricles. Abbreviations as in Figure 3.

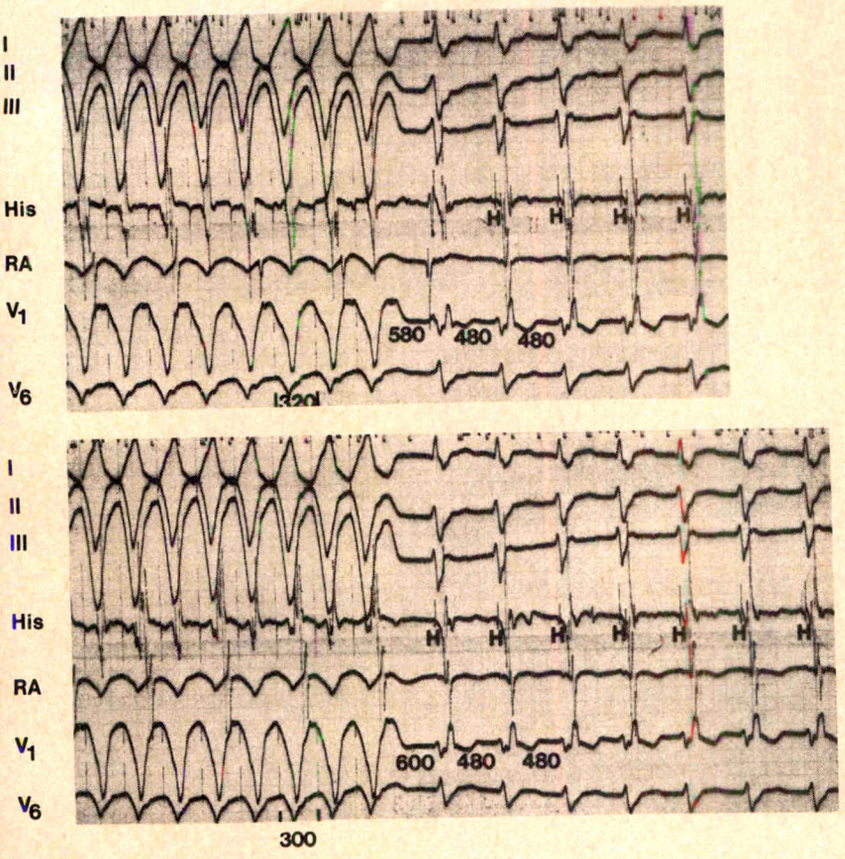


FIGURE 8. Same patient as in Figure 5. Recordings showing the failure of "overdrive" pacing to terminate tachycardia in contrast to the single ventricular stimulus shown in Figure 5. Of the many rates used during "overdrive" pacing, pacing at cycle lengths of 320 msec **(top panel)** and 300 msec **(lower panel)** are shown. Abbreviations as in Figure 3.

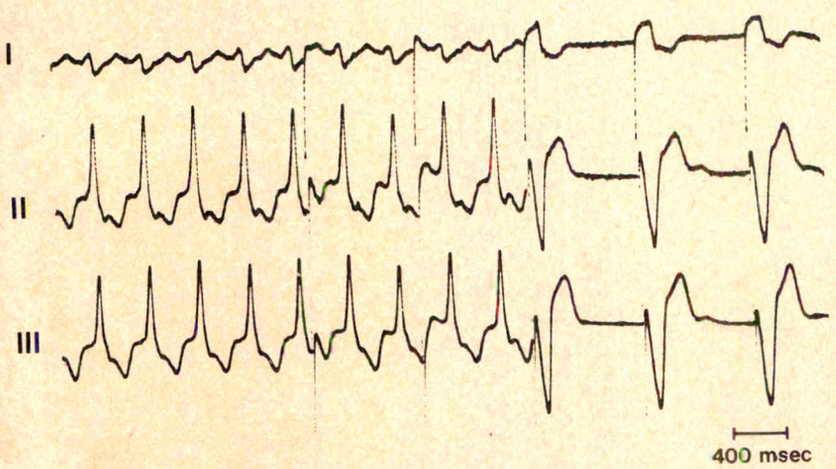


FIGURE 9. Electrocardiogram, leads I, II and III, showing termination of ventricular tachycardia (rate 140/min) with a single ventricular premature complex. The patient has an implanted demand pacemaker that during tachycardia changes to a fixed rate mode when a magnet is placed over the pacemaker.

patients with atrial flutter. Seven of the 36 patients continued to have atrial fibrillation, but 29 had reversion to sinus rhythm after a shorter or longer period of atrial fibrillation.

In all four patients showing persistence of atrial flutter, the arrhythmia was classified as uncommon[28] or type 2[29] atrial flutter. The previously discussed problems with drug management have made "overdrive" pacing our treatment of choice in patients with atrial flutter.

Other types of tachycardia: It has become extremely unusual to use temporary pacing for termination of tachycardia other than atrial flutter. Occasionally short-term pacing can be used to advantage for *prevention* of tachycardias after cardiac surgery or acute myocardial infarction.

Long-Term Pacing

In patients seriously handicapped by tachycardia that cannot be controlled with drug treatment, the following modes of pacing are available for chronic treatment:

The single stimulus method ("underdrive" pacing): Ryan et al.[30] were the first to apply to long-term therapy the principle of terminating a reentry tachy-

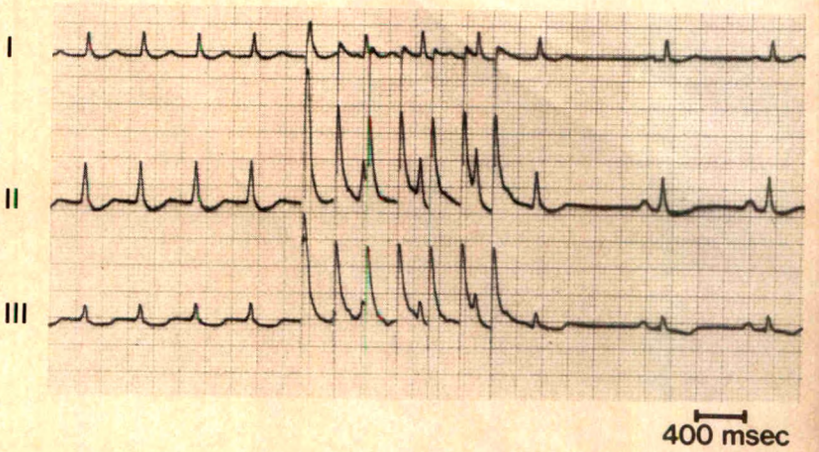


FIGURE 10. Electrocardiogram, leads I, II and III, showing termination of A-V nodal tachycardia (rate 140/min) with a rapid burst of atrial stimuli (250/min).

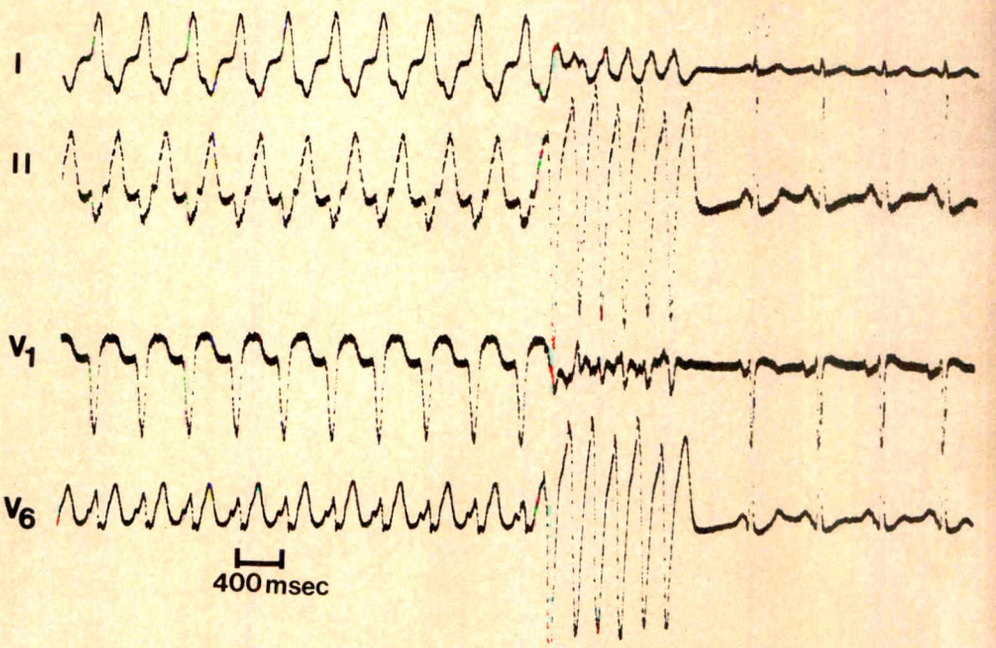


FIGURE 11. Electrocardiogram, leads I, II, V_1 and V_6, showing termination of ventricular tachycardia (rate 150/min) with a rapid burst of ventricular stimuli (300/min).

cardia with a critically timed premature stimulus. In their patient with the Wolff-Parkinson-White syndrome they positioned in the right ventricle an electrode catheter that was connected to a demand pacemaker. During tachycardia the pacemaker was converted from demand to fixed rate pacing by holding a magnet near the generator pocket. This fixed rate stimulation producing competitive pacing was continued until one of the pacemaker stimuli fell at the correct interval after a tachycardia complex, thereby terminating the tachycardia. This mode of pacing, also called "underdrive" pacing, has been successfully applied in patients with supraventricular and ventricular tachycardia,[31–34] that cannot be controlled by standard pharmacologic regimens. An example of termination of ventricular tachycardia is given in Figure 9.

Before implanting this type of pacemaker one must determine the most successful site for stimulation and demonstrate that tachycardia can indeed be terminated with a single stimulus. As indicated earlier, this is extremely unlikely when a patient's reentry circuit is confined to the A-V node and the rate of tachycardia is more than 160/min. The same is true of efforts to terminate with a single stimulus given in the right ventricle ventricular tachycardia that originates in the left ventricle and has a rate of more than 160/min. When the tachycardia circuit is large, however (for example, in the Wolff-Parkinson-White syndrome or in the presence of a concealed accessory A-V pathway), a single stimulus can often terminate tachycardia with rates of up to 200/min.

By combining the method of "underdrive" pacing with the administration of drugs, one can frequently increase the success rate of this mode of pacing. One should give a drug that slows conduction or lengthens the functional refractory period in a part of the circuit without affecting the refractory period at the site of stimulation or the conduction velocity between site of

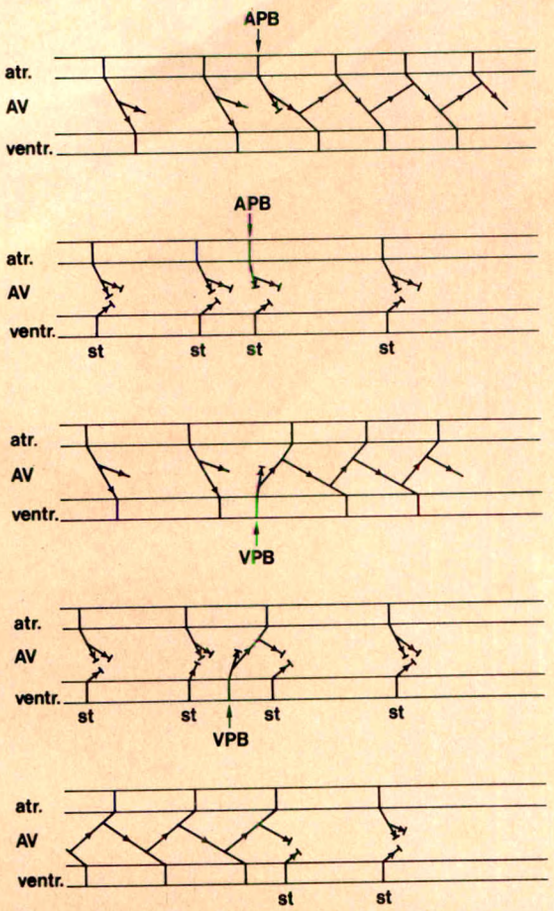


FIGURE 12. Diagram showing principle of prevention and termination of reentry A-V junctional tachycardia with an atrial synchronous pacing system. The **first and third strips** show initiation during sinus rhythm of a reentry atrioventricular (AV) junctional tachycardia by a critically timed atrial premature complex (APB) or a critically timed ventricular premature complex (VPB). **Strips two and four** indicate how reentry is prevented by synchronizing the ventricular stimulus (st) with the atrial complex. **Strip five** shows how a reentry atrioventricular junctional tachycardia can be terminated by using the same principle. atr. = atrium; ventr. = ventricle.

stimulation and the tachycardia circuit. Such a drug will decrease the rate of the tachycardia without interfering with the ability of the paced impulse to enter the tachycardia circuit. Digitalis and propranolol are examples of drugs that can be used for this purpose in patients whose A-V node is incorporated in the tachycardia circuit.

"Overdrive" pacing: As discussed previously, reciprocal tachycardia can frequently be terminated with pacing at rates in excess of the rate of the tachycardia. These observations have resulted in the development of pacemakers that are able to stimulate at a high rate and that can be activated by the patient. Originally these pacemakers were introduced for use in the atrium to interrupt supraventricular tachycardia,[35–37] but the same principle has recently been applied in the ventricle to terminate ventircular tachycardia.[38] Preferably this type of pacemaker should give a preset number (a "burst") of rapid pacing impulses. Examples of termination of supraventricular and ventricular tachycardia by patient-activated implanted radio-frequency transmitted "burst" pacemakers are given in Figures 10 and 11.

Before implantation of the pacing unit a careful electrophysiologic study must be made (1) to demonstrate the ability of rapid atrial pacing to terminate the tachycardia, (2) to select the most appropriate stimulation site, and (3) to exclude the presence of an accessory A-V pathway with a short refractory period. In patients with preexcitation, the length of the refractory period of the accessory pathway must be determined because rapid atrial pacing may induce atrial fibrillation. The latter arrhythmia can be followed by life-threatening high ventricular rates in patients with preexcitation and a short refractory period of the accessory pathway.[39]

Sequential pacing: To start reentry, tissue in the reentry pathway must be excitable for the initiating impulse to propagate. Making the reentry pathway refractory ahead of this impulse prevents completion of the reentry loop. This principle has been used in patients with reciprocal A-V junctional tachycardia.[4,13,40] As shown in Figure 12, by synchronizing ventricular depolarization to atrial activation the premature complex that used to be able to initiate reentry is now followed by ventricular activation invading the opposite end of the reentry circuit, thereby preventing initiation of tachycardia. The time interval between the triggering and induced impulse has to be derived from a stimulation study before implantation of the pacing unit.

Although this technique is theoretically attractive, there are important limitations to its application: (1) The A-V nodal properties can be such that the atrial premature complex initiating A-V junctional tachycardia occurs so early that it falls within the refractory period of the pacemaker. As pointed out by Spurrell,[4] this problem can be overcome by increasing the refractory period of the A-V node with use of drugs. (2) When the reentry circuit is confined to the A-V node, and especially when the tachycardia rate is high, the ventricular impulse may not be able to invade the reentry circuit. (3) When the time required for retrograde conduction is long, the triggered ventricular impulse may be conducted over the retrograde part of the pathway and arrive at the proximal common pathway at a time when this area has recovered excitability. Such an event leads to perpetuation of tachycardia. This is probably why in our experience this mode of pacing is frequently unsuccessful in patients with A-V junctional tachycardia of the so-called incessant type,[41] an arrhythmia in which the circulating impulse characteristically requires a long time to traverse the retrograde limb of the circuit.

New Developments

At present, the long-term application of both the "underdrive" and "overdrive" method of pacing requires the cooperation of the patient. The patient has to recognize the arrhythmia and should be aware of the

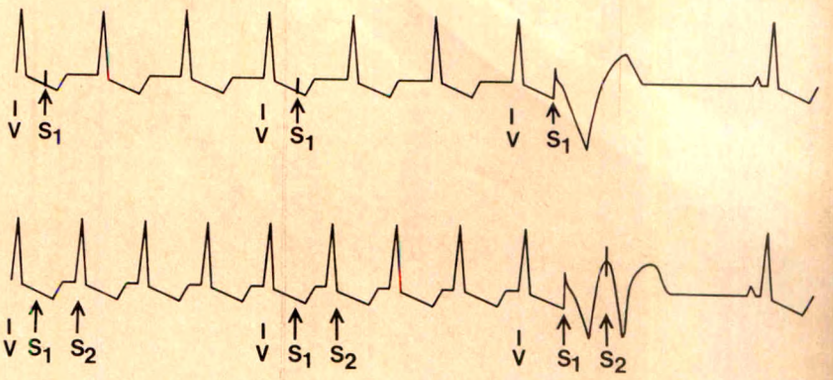


FIGURE 13. Principle of the so-called scanning pacemaker.[4] Depending upon the rate of the tachycardia, one **(upper tracing)** or two **(lower tracing)** closely coupled premature stimuli are given to terminate tachycardia. The first premature stimulus (S_1) **(top)** is given early in the tachycardia cycle; succeeding premature stimuli are given later with an increment of 5 msec until capture of the ventricle results in termination of tachycardia. The **lower tracing** shows the same principle using two premature stimuli (S_1 and S_2). The distance between S_1 and S_2 remains the same.

importance of careful placement of the transmitting unit over the receiver. He must also be able to recognize successful conversion of the arrhythmia.

A more ideal approach would be use of an implantable pacemaker able to recognize tachycardia and to initiate the necessary mode of stimulation for its termination. Apart from the "burst" pacemaker, a "scanning" pacemaker as suggested by Spurrell[4] could be an example of such a device. As shown in Figure 13, after the onset of tachycardia an extrastimulus is given after a preset number of tachycardia complexes. The extrastimulus results after a preset delay following the triggering intracardiac potential obtained from the catheter electrode. This delay is set to occur within the refractory period of the chamber being stimulated. After a preset number of tachycardia complexes the next stimulus occurs 5 msec later than the preceding one. In this way the cardiac cycle is scanned in 5 msec intervals. This will result in an appropriately timed premature complex terminating the tachycardia.

As discussed, termination of tachycardia with a single premature complex requires stimulation close to the tachycardia circuit and usually relatively low rates during tachycardia. Therefore with use of the scanning principle two or even three premature complexes may be required to terminate tachycardia of higher rates. Guize et al.[42] devised another principle of pacing called orthorhythmic pacing, which is characterized by pacing at intervals related to the length of the preceding cardiac cycle. Pacing intervals and number of paced complexes can be programmed. The beneficial use of this mode of pacing in patients with tachycardia has been demonstrated.

Both the orthorhythmic pacemaker and the scanning pacemaker require individual design of pacing intervals and number of paced complexes. This obviously makes these units complicated, expensive and vulnerable to failure and has so far prevented the development of the orthorhythmic and the scanning pacemaker units for long-term use in an implantable form. In view of the large number of patients with tachycardia who constantly live under the fear of attacks and their dependency on medical help and who are condemned to lifelong medication, we believe that active involvement of pacemaking firms in the development of these types of implantable pacemakers is urgently needed.

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Surgical Treatment of Arrhythmias: Current Status and Future Directions

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A variety of surgical interventions have evolved for the treatment of intractable or life-threatening arrhythmias unresponsive to conventional pharmacologic or pacemaker therapy. Supraventricular arrhythmias associated with rapid ventricular responses can be indirectly treated with ablation of the atrioventricular conduction system and insertion of a pacemaker. Ventricular tachyarrhythmias have previously been treated with sympathectomy, resection of tissue or revascularization. More recent approaches include the simple ventriculotomy, encircling endocardial ventriculotomy, cryosurgical ablation and insertion of the automatic implantable defibrillator. Refinement of methods to localize more precisely the origin of ventricular arrhythmias may allow design of more direct surgical procedures. The surgical treatment of arrhythmias related to the preexcitation syndromes remains the model of electrophysiologic surgery. It is now feasible to divide accessory pathways with a high degree of success and at low risk in selected patients.

Remarkable advances in the medical management of cardiac arrhythmias have been achieved in the past decade. Nevertheless, despite the availability of new pharmacologic agents and innovative pacing techniques, these measures are occasionally either ineffective or undesirable because of side effects. This communication reviews currently available surgical techniques for modifying or ablating rhythm disturbances. These include procedures relating to (1) supraventricular and junctional tachyarrhythmias, (2) ventricular arrhythmias, and (3) arrhythmias associated with the preexcitation syndrome. The therapeutic alternatives include ablation of the site of origin of arrhythmia (excision or destruction in situ) or modification of the milieu of the site of origin (autonomic manipulation, revascularization and other measures). For supraventricular arrhythmias, indirect therapy is available in the form of interruption of the normal conduction system, thereby protecting the ventricles from inappropriate rate responses.

Supraventricular and Junctional Tachyarrhythmias

The ideal approach to treating an arrhythmia arising in the atrium would be direct ablation of the area responsible. Coumel et al.[1] reported a case of ectopic atrial tachycardia in which the atrium was mapped and the focus of tachycardia localized and subsequently destroyed by cautery. Unfortunately, in many instances the disease process is not sufficiently localized to permit this approach. For example, in patients with sinus node disease reentry may occur in the region of the sinus node although pathologic studies generally show more widespread disease in the atrium and the junction, resulting in a predisposition to atrial fibrillation and conduction disorders.

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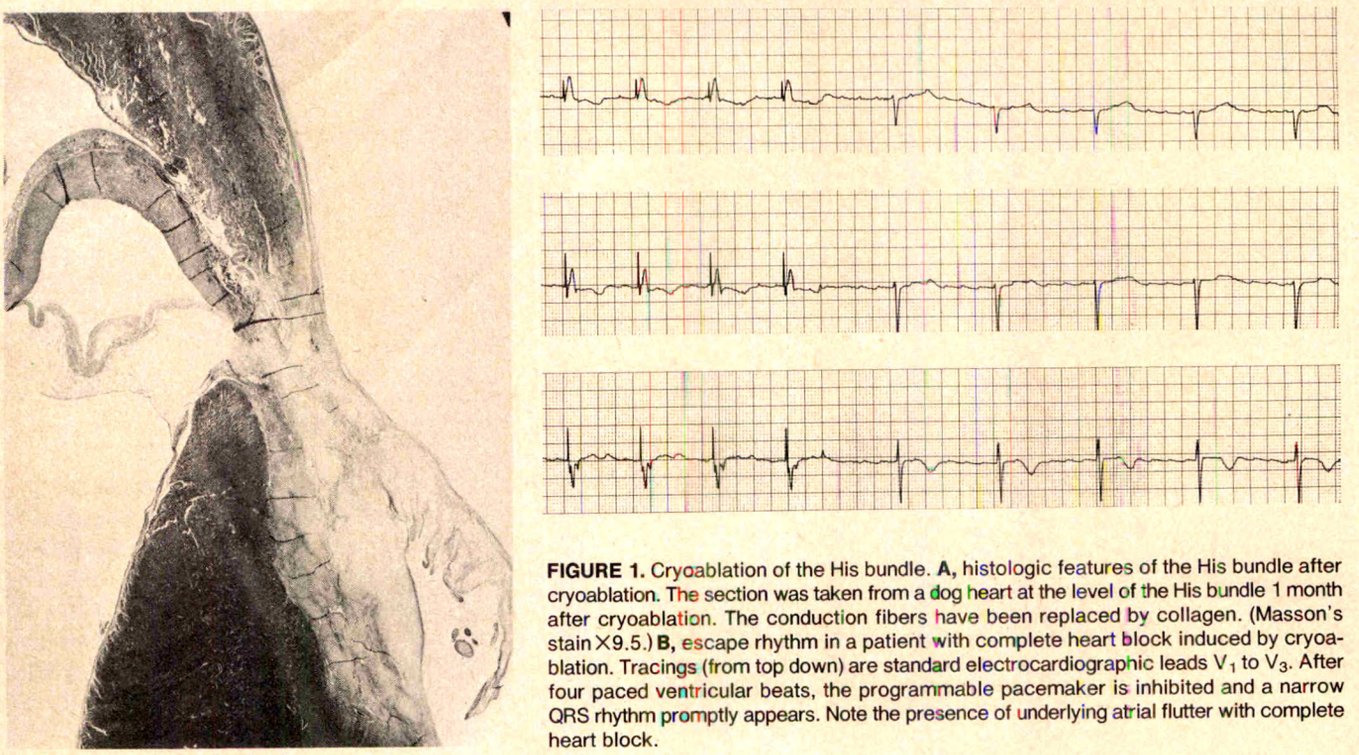


FIGURE 1. Cryoablation of the His bundle. **A,** histologic features of the His bundle after cryoablation. The section was taken from a dog heart at the level of the His bundle 1 month after cryoablation. The conduction fibers have been replaced by collagen. (Masson's stain ×9.5.) **B,** escape rhythm in a patient with complete heart block induced by cryoablation. Tracings (from top down) are standard electrocardiographic leads V_1 to V_3. After four paced ventricular beats, the programmable pacemaker is inhibited and a narrow QRS rhythm promptly appears. Note the presence of underlying atrial flutter with complete heart block.

Surgical interruption of bundle of His: Technically one can easily map the activity of the atrial myocardium and the His bundle.[2] Recent reports[3,4] suggest the possibility of recording activity of the sinus node, but attempts to record activity of the atrioventricular (A-V) node[5] have been less successful. With the increasing use of intraoperative mapping studies, it seems reasonable to anticipate the development of techniques that will permit the direct treatment of supraventricular and junctional rhythm disorders. Currently, ablation of the His bundle is the most generally used procedure.[6,7] Early reports concerning interruption of the His bundle emphasized ligation, cautery or dissection. Surgical ligation of the His bundle was followed by frequent recurrence of intact A-V conduction. Experimental studies suggest that conduction can persist with as little as 10 percent of the His bundle intact. Cautery denatures collagen and results in loss of tensile strength. In addition, the extent of the lesion induced by cautery is difficult to control and is irreversible. Direct dissection carries an attendant risk of damaging the tricuspid valve or aorta or of creating a septal defect. For these reasons, a cryosurgical approach[6] was developed that not only affords a simple, reliable means of producing A-V block, but also usually preserves subsidiary pacemaker function in the distal His bundle.

In this procedure, the right atrium is opened after institution of cardiopulmonary bypass, and the His bundle is localized by endocavitary mapping. A cylindrical probe with a 5 mm tip is applied to the region of the His bundle, and nitrous oxide is circulated to the tip of the probe. With expansion of the gas, cooling occurs. By controlling the rate of escape of gas from the system, the temperature in a localized area can be reduced stepwise from room temperature to −60° C with an accuracy of ±5° C. This allows an initial reduction of temperature to 0°, when reversible cessation of physiologic activity in the His bundle occurs. Reducing the temperature to −60° C for several minutes results in an irreversible block. The initial freeze is carried out over the most proximal site of recorded His bundle activity and is usually repeated one to two times. Experimental evidence suggests that repeat freezing results in more cell injury than a single freeze. The permanent lesions induced by irreversible freezing are in our experience homogeneous and well demarcated; they have no tendency to rupture, form aneurysms or promote intracardiac thrombosis (Fig. 1). These features are undoubtedly related to the known resistance of vascular elements, collagen and fibroblasts to hypothermal injury. The prompt appearance of A-V block with creation of the initial reversible lesion at 0° C has correlated well with persistence of block after creation of an irreversible lesion.

Cryoablation of the His bundle has been attempted in 16 patients to date. In 14 of these, A-V block was promptly achieved with the initial application of 0° C to the region of the His bundle, and only 1 of the 14 had a subsequent return to sinus rhythm. In the two remaining patients, block was not achieved with the initial application of 0° C. Both patients underwent attempted dissection of the His bundle but, despite extensive dissection, A-V conduction remained intact in both; however, in one, the A-V node was sufficiently modified that no further arrhythmias (that is, reentry in the A-V node) occurred. These 14 patients have now been fol-

lowed up from 1 to 28 months (mean 15 ± 8.4) and, on inhibition of their pacemaker (Fig. 1B), have demonstrated a subsidiary escape rhythm of 40 to 50 beats/min with QRS complexes comparable with those present during sinus rhythm before the occurrence of block. Electrophysiologic studies in selected patients have demonstrated persistence of a small His deflection with a short H-V interval preceding these escape beats, suggesting an origin in the distal His bundle.

Experience in one of the patients with reentry in the A-V node suggests that it may be possible to modify the A-V node or its inputs in such a way as to prevent reentry. After an unsuccessful attempt to dissect the His bundle in this patient, sinus rhythm returned with first degree A-V block. Restudy demonstrated inability to initiate any reciprocating tachycardia despite integrity of anterograde and retrograde conduction.

For the sake of completeness it should be noted that cardiac sympathectomy enjoyed a measure of success in the early reports on surgical attempts to relieve supraventricular tachycardia. Leriche and Fontaine[8] were the first to treat successfully two patients with recurrent supraventricular tachycardia by means of bilateral thoracic sympathectomies. Subsequently, White et al.[9] treated six patients with supraventricular tachycardia with unilateral or bilateral sympathectomy or alcohol block.

Ventricular Tachyarrhythmias

Development of an effective surgical remedy for recurrent ventricular tachyarrhythmias would undoubtedly have great impact in view of the malignant nature and recalcitrance of some of these rhythm disorders. Unfortunately, the substrate and mechanism of ventricular arrhythmias are poorly understood and probably differ according to the underlying disease process. A variety of therapeutic interventions have been empirically introduced; a relatively high failure rate is reported with most.

Sympathectomy: The potential usefulness of bilateral sympathectomy in the treatment of ventricular arrhythmias is suggested by observations that animals with sympathectomy or cardiac denervation have a reduced incidence of ventricular arrhythmias and death after experimental myocardial infarction.[10,11] The use of sympathectomy in the treatment of arrhythmias was initially limited to management of supraventricular arrhythmias.[8,9] Estes and Izlar[12] reported successful treatment of ventricular tachycardia with bilateral cardiac sympathectomy in 1961. This report was followed shortly by others.[13–16] Zipes et al.[13] successfully treated a patient with paroxysmal ventricular tachycardia by combining atrial pacing with sympathectomy. Lloyd and associates[15] reported that bilateral sympathectomy facilitated medical management of paroxysmal ventricular tachycardia despite previous refractoriness to propranolol. Access to both thoracic cavities is required for this operation because the stellate ganglion through T7 should be excised on both sides. A bilateral Horner's syndrome results. Review of several small series indicates that up to 58 percent of patients can be relieved of arrhythmia by sympathectomy.[17]

In patients with Q-T prolongation, left cervicothoracic sympathectomy has been reported to return the Q-T interval to normal, preventing recurrent arrhythmias.[18]

Resection of tissue: Although the association between ventricular arrhythmias and ventricular aneurysms was recognized in the early 1900's,[19–21] the first successful resection of a ventricular aneurysm with cure of the associated tachycardia was not undertaken until 1956 by Bailey and reported by Couch in 1959.[22] Subsequently there have been several reports of intractable ventricular arrhythmias successfully treated by aneurysmectomy[14,17,19–44] or infarctectomy.[45–52] The operative mortality rate varies widely, with the highest rate reported in patients with severe congestive failure or evidence of recent infarction. In general, a 10 percent mortality rate can be anticipated. The postoperative mortality rate ranges from 10 to 25 percent, followed by a late mortality rate reported as high as 50 percent in 3 years. The long-term prognosis clearly depends on the extent, distribution and progression of occlusive coronary artery disease. Aneurysm resection in concert with attempts at revascularization may enhance the likelihood of a successful outcome.

Revascularization: By virtue of its ability to increase blood flow to areas of ischemia, aortocoronary bypass surgery can potentially correct factors predisposing to serious arrhythmia. Several reports[17,53–69] attest to the ability of this procedure to terminate ventricular arrhythmias. Ricks et al.[68] reported an 80 percent in-hospital mortality rate when operation was performed within 1 month of acute infarction, whereas operation performed more than 1 month after infarction had a 20 percent mortality rate. Surgical treatment that included myocardial resection had significantly less mortality than treatment that did not. The series of Ricks et al. demonstrated, in addition, long-term survival despite persistence of ventricular arrhythmias. Asymptomatic runs of ventricular tachycardia were also noted by Graham et al.[61] in a series of patients whose condition was considered well controlled with medical therapy. Giacchino et al.[64] reported a high mortality rate in patients with severe coronary artery disease, marked left ventricular dysfunction and recurrent ventricular tachycardia whether surgical or medical treatment was employed. Waxman and co-workers[65] studied 14 patients who experienced the onset of intractable ventricular tachycardia an average of 4 weeks after myocardial infarction. Surgical therapy consisting of resection of noncontractile areas combined when feasible with revascularization resulted in a 50 percent survival rate over a follow-up period of 3 to 12 months, whereas six patients not treated surgically died within 1 week of hospital discharge.

The results obtained in the small number of patients treated with revascularization support the concept that reversible left ventricular dysfunction with associated

refractory ventricular tachycardia can in some instances be successfully treated in this manner although it is not clear whether the beneficial effect is mediated mechanically or electrophysiologically. Unfortunately, not all patients reported on have undergone subsequent angiography to demonstrate graft patency, and it is possible that interim myocardial infarction occurred in some, abolishing further episodes of arrhythmia. Revascularization of patients presenting with serious ventricular arrhythmias refractory to medical therapy and associated with significant lesions in the coronary vasculature deserves further clinical trial. Myocardial resection should be considered in conjunction with revascularization when focal aneurysms or discrete areas of akinetic or dyskinetic myocardium are detected. Careful attention must be paid in future trials to the manner of selection and to the nature of the medical therapy given after operation.

The variable results obtained with the interventions described suggest that, although all procedures enjoy some unequivocal successes, the outlook for a favorable result is not uniform in any particular case, and the overall results are less than optimal. This may reflect the nonuniformity of the underlying disease process, its relentless progression in some cases, and our ignorance of the underlying mechanisms. Nevertheless, the search continues for new ways to treat such ventricular arrhythmias effectively. One approach currently under investigation in several centers is the use of preoperative and intraoperative electrophysiologic study to define more precisely the nature of the mechanism and site of origin of ventricular arrhythmia in various diseases.

Role of preoperative and intraoperative studies: At least two major mechanisms of arrhythmia formation—automaticity and reentry—can be identified, but both can potentially exist in the same patient. The relative role of each in the pathogenesis of any given patient's rhythm disturbance may be difficult to discern. Clinically, the ability to initiate and terminate arrhythmia by programmed premature stimulation has been interpreted as evidence of a reentry phenomenon.[70,71] Recent in vitro studies[72] suggest that a type of repetitive activity not conforming to the classic model of reentry can be initiated with programmed stimulation in isolated tissues in the setting of certain electrolyte imbalances or on exposure of the preparation to high concentrations of catecholamines. Nevertheless, the application of programmed stimulation to elicit arrhythmias remains empirically useful. It allows the arrhythmia to be elicited for purposes of diagnosis, provides a means of assessing the efficacy of drug therapy and, in some cases, suggests the utility of a pacemaker device to control recurrences. Finally, the extrastimulus technique has been used in selected patients to elicit the arrhythmia in the operating room where epicardial, intramural and endocardial mapping techniques have been used to attempt localization of the site of origin of arrhythmia. As will be discussed, the introduction of complex methodology may be necessary if mapping is to become applicable to the study of ventricular tachycardia and fibrillation in general. Such study has been most productive in the formulation of the operative approach known as "simple ventriculotomy."

Simple ventriculotomy: Guiraudon et al.[73] first reported in 1974 successful treatment of resistant ventricular tachycardia in the absence of coronary artery disease by means of a simple ventriculotomy. Preoperative electrophysiologic study was performed to characterize the alterations necessary to induce ventricular tachycardia and to test the applicability of drug and pacemaker therapy. Thirteen patients have subsequently undergone epicardial mapping during sinus rhythm and during ventricular tachycardia.[74–76] Epicardial mapping during sinus rhythm generally demonstrated areas of delayed activation (postexcitation phenomenon), and these areas were noted to be the apparent site of origin of ventricular tachycardia when the latter was induced. A transmural ventriculotomy 4 to 5 cm in length was performed at each point of emergence of ventricular tachycardia; when the latter was located in thin-walled zones that could be easily resected and where postexcitation was detected, ventriculotomy was associated with limited resection of such areas. Of these 13 patients, only 1 had a relapse of ventricular tachycardia after operation. This patient demonstrated at least seven sites of ventricular tachycardia and died with low output failure on the fifth postoperative day. A second patient with Uhl's anomaly (paper-thin right ventricle) died with low output failure on the eighth postoperative day without recurrence of ventricular tachycardia. All other patients are free of arrhythmia after a follow-up period of 1 month to 4 years. Similar results were obtained by Spurrell et al.[77–79] using a comparable technique.

In a second group of three patients[74–76] in whom ventricular tachycardia could not be initiated with pacing techniques, ventriculotomy was unsuccessful in abolishing the arrhythmia. The investigators suggested that the point of origin of ventricular tachycardia demonstrated by mapping was probably situated on the reentrant limb, and ventriculotomy in this general area apparently interrupted or modified the reentry circuit. The failure encountered in patients whose ventricular tachycardia was not inducible by pacing suggested to these investigators that an ectopic focus was present, and they now consider such patients unsuitable for simple ventriculotomy.

Fontaine et al.[75] attempted to extrapolate their method of simple ventriculotomy to the setting of ventricular tachycardia after myocardial infarction. The operative findings and the clinical results differed markedly from those obtained when the procedure was performed in the setting of a cardiomyopathy. Thus, in a group of 13 surgically treated patients with ventricular tachycardia related to ischemic heart disease, evidence of delayed potentials was found in only 1 patient. The epicardial map during ventricular tachycardia was uninterpretable in 11 of 13; ventriculotomy was successful in only 1 of the remaining 2 patients. These findings suggest that the difficulty encountered in the attempts to map the arrhythmias of these patients was related to

coronary artery disease, which accounted for the difficulty in applying simple ventriculotomy in this patient group.

More encouraging results were recently reported by Guiraudon et al.[80] and Escande[81] in patients with ventricular tachycardia secondary to ischemic heart disease using the technique called "encircling endocardial ventriculotomy."

Encircling endocardial ventriculotomy: The procedure of encircling endocardial ventriculotomy was performed in five patients with resistant ventricular tachycardia presenting 1 month to 8 years after myocardial infarction.[80,81] A reentry mechanism was suggested by preoperative electrophysiologic study in all patients. During cardiopulmonary bypass, the left ventricle was entered through the area of infarction characterized by a thin fibrous scar. A transmural ventriculotomy perpendicular to the wall was carried out along the limits of the endocardial fibrosis that separated the abnormal from the normal myocardium (Fig. 2). The fibrosis was noted to involve the parietal ventricular wall, the papillary muscles or the septum singly or in combination. Over the parietal portion of the ventricular wall, the encircling endocardial ventriculotomy was a full thickness section sparing the epicardium and the coronary vessels. When the septum was involved, the ventriculotomy was approximately 1 cm in depth but not transmural. The incision was repaired with a running suture and the ventricle closed in the usual way. The rationale for this procedure was that the reentry presumably arose in the border zone of infarction between the normal and ischemic zones, and the incision thus abolished potential reentry loops along this boundary. Antiarrhythmic therapy was discontinued after operation, and no recurrence was noted during a follow-up period of 6 to 24 months. The initial success obtained in this small group of patients deserves further study. The long-term results of such a ventriculotomy must be ascertained. The procedure is attractive theoretically because it allows an approach to the papillary muscles without altering valve function and allows the septum to be modified without resection.

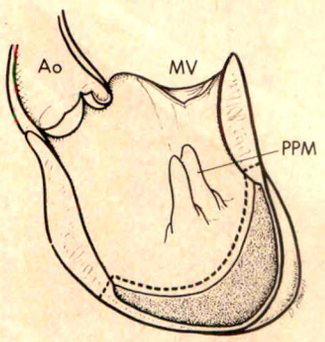


FIGURE 2. Encircling endocardial ventriculotomy of Guiraudon. A cross section of the left ventricle is shown with an area of extensive subendocardial infarction indicated by **stippling.** The **dashed line** indicates the area at the border of infarction where the ventriculotomy is performed. Ao = aorta; MV = mitral valve; PPM = posterior papillary muscle.

Section of the bundle branches: Spurrell et al.[79] described four patients who manifested a reentry mechanism in the bundle branches that was thought to be the basis of their recurrent ventricular tachycardia. Three of these patients underwent operation. The anterior radiation of the left bundle branch was divided in two of the three. One of these two patients also underwent resection of a large aneurysm of the left ventricle and died at operation. The other patient had mitral valve replacement in concert with aortocoronary bypass grafting and remained free of arrhythmia postoperatively. In view of the complex nature of the operative intervention, the success in the latter patient cannot be ascribed with assurance to the lesion induced in the left bundle branch.

Prolapsing mitral valve: Cobbs and King[82] reported the effect of mitral valve replacement in four patients

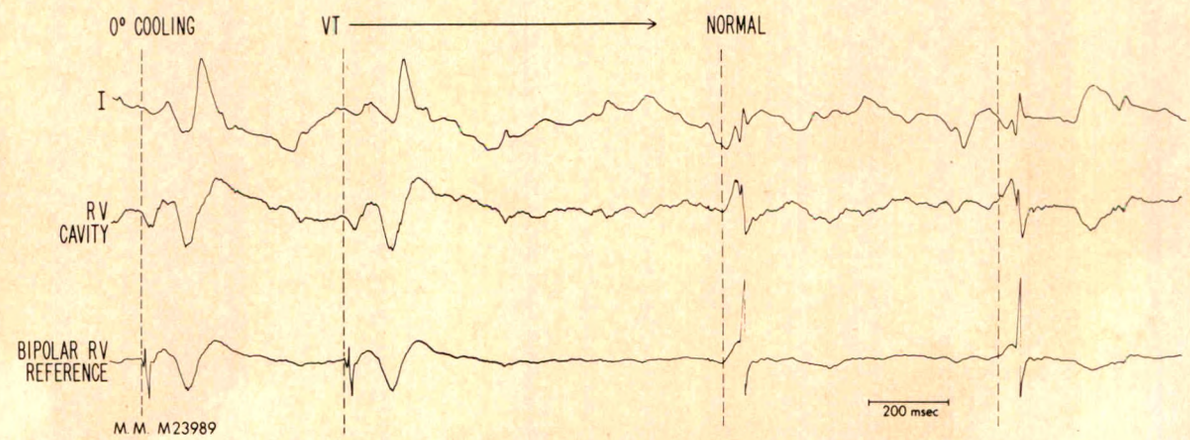


FIGURE 3. Termination of ventricular tachycardia by cooling. Tracings (from top down) are standard electrocardiographic lead I, a cavity potential recorded from the right ventricle (RV) and a bipolar electrogram recorded from the right ventricle adjacent to the site of origin of tachycardia. With cooling to 0° C, the ventricular tachycardia terminates and sinus rhythm resumes.

with mitral valve prolapse and life-threatening ventricular arrhythmias. Two of these patients continue to receive drug therapy after demonstrating ventricular tachycardia and fibrillation without drugs. Two others remain free of arrhythmias. In one of these, epicardial mapping at the time of operation suggested an irritable focus in the region of the posterior papillary muscle but a sustained tachyarrhythmia was not studied.

Sealy and Oldham[17] reported on the effect of sympathectomy for arrhythmias related to the mitral valve prolapse syndrome in three patients. One patient is free of arrhythmia, but two others have persistent episodes of ventricular tachycardia.

Resection of cardiac tumor: Engle et al.[83] reported successful abolition of recurrent ventricular tachycardia in two children after excision of a left ventricular tumor.

Cryosurgery: The successful application of cryosurgery to the ablation of His bundles[6] and accessory pathways[84,85] prompted our use of this technique in a patient with recurrent ventricular tachycardia associated with a variant form of scleroderma.[86] The site of origin of ventricular tachycardia was localized to the anterior wall of the right ventricle and was demonstrated to activate well before the onset of the surface QRS complex. Surface cooling of this area to 0° C promptly resulted in termination of tachycardia (Fig. 3) with reappearance of tachycardia on rewarming. Transmural cooling to −60° C resulted in irreversible ablation of the focus. The lesion produced by this technique was experimentally found to be very discrete[87] and thus requires precise localization of the origin of arrhythmia to be effective. This technique has the advantage that diagnostic information can be obtained in a reversible way before a definitive lesion is created.

Cautery: A case of localization and cautery destruction of a ventricular focus was reported by Petitier et al.[88]

Automatic implantable defibrillator: Mirowski and Mower and their co-workers[89,90] reported the development of an implantable low energy demand unit for defibrillating the ventricles. Initially introduced as a transvenous catheter electrode system, the device in its present form requires surgical implantation of special electrodes on the heart. The energy required for defibrillation has been decreased 15 watts/sec or less. An experimental prototype that is completely implantable has been developed.[91] Further pursuit of this unusual concept may one day furnish a possible treatment for certain high risk patients refractory to all other measures.

Cardiac transplantation: Transplantation of the heart should be mentioned as a possible mode of therapy in selected patients with intractable life-threatening arrhythmias not amenable to other forms of therapy.

Future directions in the surgery of ventricular arrhythmias: Design of a surgical procedure for the effective treatment of ventricular arrhythmias will require greater understanding of the underlying mechanisms and refinement of our ability to localize precisely the site of origin of these arrhythmias. It was initially hoped that epicardial mapping would provide a useful tool in guiding the surgeon. In some settings, epicardial

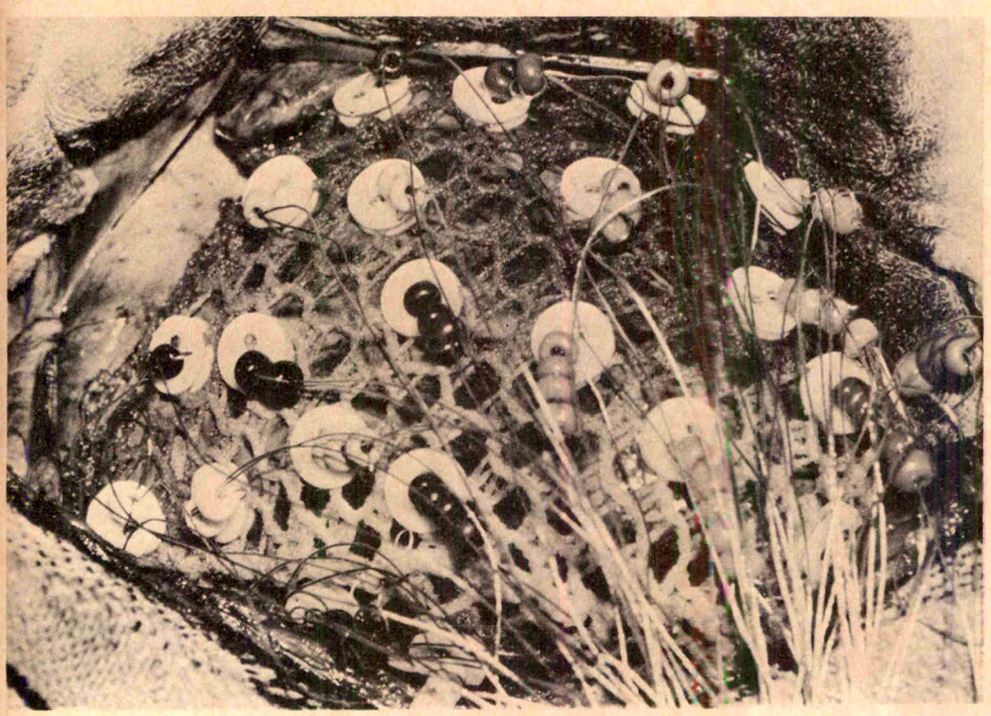


FIGURE 4. Sock electrode for epicardial mapping. The nylon mesh sock is shown with button electrodes placed in the mesh. Colored beads are used to identify the electrode sequence.

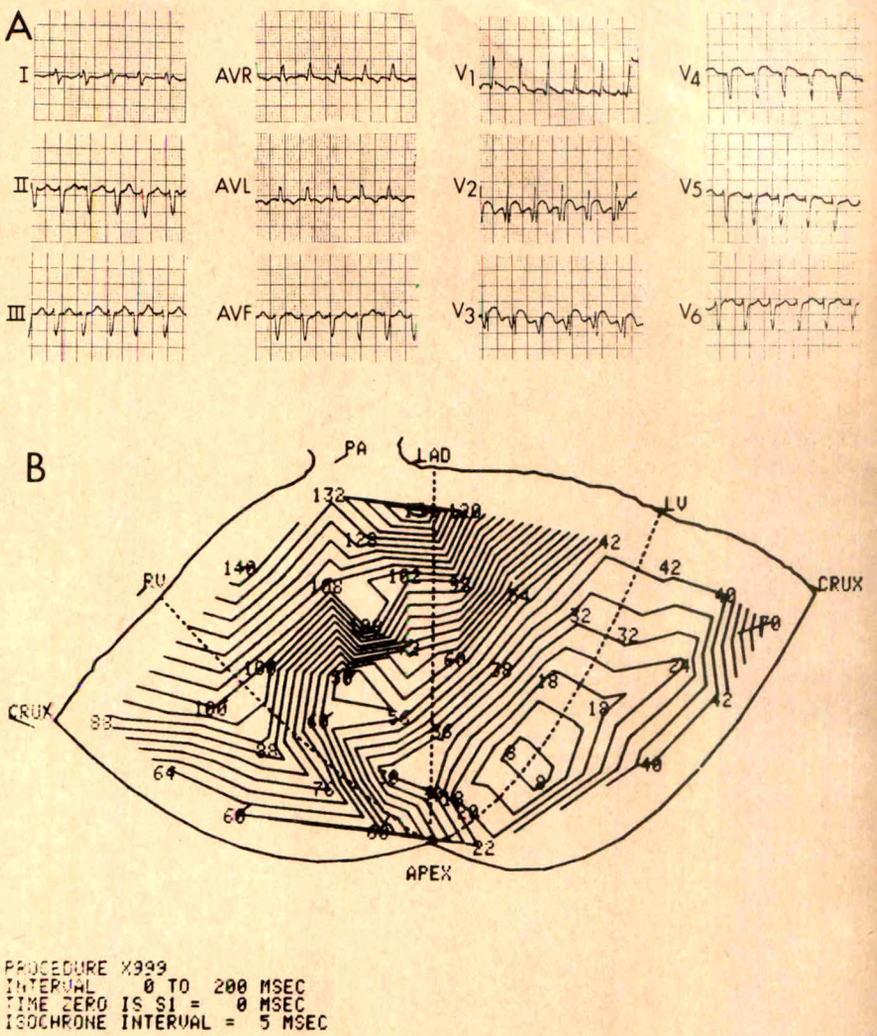


FIGURE 5. Epicardial mapping of ventricular tachycardia. **A,** 12 lead electrocardiogram during ventricular tachycardia. **B,** computerized map of the sequence of epicardial activation during a single beat of tachycardia. The heart is shown unfolded as if cut along the posterior descending coronary artery. Isochronous lines have been plotted for every 5 msec of activation, and the entire map is referenced to the onset of the surface QRS complex. The earliest epicardial activation occurs near the apex over the parietal portion of the lateral left ventricle. CRUX = region where the posterior interventricular groove and the atrioventricular groove join; LAD = left anterior descending coronary artery; LV = left ventricle; PA = pulmonary artery; RV = right ventricle.

mapping indeed proved a useful adjunct to this type of surgery.[43,69,73–79,86,88] Many arrhythmias, especially those related to severe coronary artery disease, are fleeting and difficult to elicit in the operating room and tend to be rapid and unstable, frequently deteriorating to ventricular fibrillation. Currently available mapping techniques require individual epicardial sites to be sampled consecutively and timed relative to a reference electrode. This requires that a stable unifocal ventricular tachycardia be present in the operating room. At best this accomplishes only an indirect localization based on the breakthrough of the activation front on the epicardium. The limitations of this technique in the study of ventricular tachycardia have been emphasized.[92–94] Furthermore, the time constraints encountered during cardiopulmonary bypass preclude extensive mapping.

One approach is to record multiple sites simultaneously. To this end, we have developed a sock electrode[95,96] (Fig. 4) to permit rapid data acquisition. The data are digitized and analyzed on line by a computer. An experimental prototype has been developed that allows a complete epicardial map to be obtained with the single beat of tachycardia (Fig. 5). The epicardial map so obtained allows placement of a detailed surface grid of electrodes and, ultimately, placement of a limited number of transmural multielectrode needles to define transmural and endocardial activation. Preliminary results obtained in dogs subjected to myocardial infarction have demonstrated the feasibility of localizing the origin of ventricular tachycardia to the endocardium underlying the border zone of the infarction. It is hoped that further work of this type will allow more precise localization of arrhythmias, setting the stage for development of more discrete surgical intervention directed at the pathogenetic mechanism.

Arrhythmias Related to Preexcitation Syndromes

The surgical treatment of preexcitation syndromes represents the model of electrophysiologic surgery. This effort has been facilitated by the ability to define and localize accessory pathways preoperatively. The sub-

stantial advances in our understanding of the preexcitation syndromes in the last decade are summarized elsewhere.[97,98] Significant modifications in the surgical technique have been introduced as a result of insights gained from study of available histologic material, advances in the methods of epicardial mapping, and the correlation of mapping with the results of surgical intervention in patients previously operated on. It is now feasible to divide accessory pathways with a high degree of success in patients with refractory, disabling or life-threatening arrhythmias related to the preexcitation syndromes. These syndromes continue to provide the best studied model of reentry in man.

Just as many of the advances in the surgical treatment of preexcitation were made possible by a greater understanding of the underlying electrophysiology of the syndromes, it is probable that major advances in new surgical treatments for other arrhythmias must await our understanding of the basic pathophysiology of these arrhythmias.

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Clinical, Electrocardiographic and Electrophysiologic Observations in Patients With Paroxysmal Supraventricular Tachycardia

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Seventy-nine patients without ventricular preexcitation but with documented paroxysmal supraventricular tachycardia were analyzed. Electrophysiologic studies suggested atrioventricular (A-V) nodal reentrance in 50 patients, reentrance utilizing a concealed extranodal pathway in 9, sinus or atrial reentrance in 7 and ectopic automatic tachycardia in 3. A definite mechanism of tachycardia could not be defined in 10 patients (including 7 whose tachycardia was not inducible). The three largest groups with inducible tachycardias were compared in regard to age, presence of organic heart disease, rate of tachycardia, functional bundle branch block during tachycardia and relation of the P wave and QRS complex during tachycardia. A-V nodal reentrance was characterized by a narrow QRS complex and a P wave occurring simultaneously with the QRS complex during tachycardia. Reentrance utilizing a concealed extranodal pathway was characterized by young age, absence of organic heart disease, fast heart rate, presence of bundle branch block during tachycardia and a P wave following the QRS complex during tachycardia. Sinoatrial reentrance was characterized by frequent organic heart disease, a narrow QRS complex and a P wave in front of the QRS complex during tachycardia.

In conclusion, a mechanism of paroxysmal supraventricular tachycardia could be defined in most patients. Observations of clinical and electrocardiographic features in these patients should allow prediction of the mechanism of the tachycardia.

In the early 1970's it was demonstrated that most patients with paroxysmal supraventricular tachycardia responded to atrial coupled stimulation with induction of atrial echoes and reproduction of tachycardia.[1–3] It was noted that induction of echoes was related to achievement of a critical atrioventricular (A-V) nodal conduction time, suggesting A-V nodal reentrance. It was implied that most or all paroxysmal supraventricular tachycardia occurring in patients without ventricular preexcitation reflected sustained A-V nodal reentrance. Subsequent studies demonstrated additional electrophysiologic mechanisms responsible for the occurrence of tachycardia, such as A-V reentrance utilizing concealed extranodal pathways,[4–8] sinus reentrance,[9,10] atrial reentrance[10] and atrial ectopic firing.[11,12]

Until the present study, there have been no investigations of a large series of patients with paroxysmal supraventricular tachycardia (without manifest preexcitation) in whom reproducibility and the electrophysiologic mechanism responsible for the arrhythmia were systematically studied. In addition, the clinical and electrocardiographic features associated with specific mechanisms of paroxysmal tachycardia have not been delineated. In this study, we report clinical electrocardiographic

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observations in a large consecutively studied series of patients with paroxysmal supraventricular tachycardia and relate these findings to results of electrophysiologic study.

Methods

Patient selection: Criteria for inclusion in the study included (1) a history of electrocardiographically documented recurrent paroxysmal supraventricular tachycardia[13]; (2) absence of evidence of preexcitation in all available electrocardiograms (most patients had four or more electrocardiograms for review); and (3) performance of extensive electrophysiologic studies using programmed atrial and ventricular stimulation and endocardial mapping during induced tachycardia. Seventy-nine patients studied between July 1972 and January 1977 fulfilled these criteria. The group consisted of 45 male and 34 female subjects aged 12 to 81 years (mean ± standard deviation 52 ± 16).

Electrophysiologic studies: These studies were performed during the postabsorptive, nonsedated state. Informed written consent was obtained from all patients. Cardiac drugs were discontinued at least 48 hours before the study. A tripolar electrode catheter was percutaneously passed through a femoral vein and placed across the tricuspid valve for His bundle recording.[14] A second hexapolar catheter was placed at the right ventricular apex through an antecubital vein. The distal two electrodes (tip) were utilized for ventricular pacing, the middle two electrodes (10 cm from the tip) for recording of right atrial electrograms, and the proximal two electrodes (13.5 cm from the tip) for right atrial pacing. A third bipolar catheter with an interelectrode distance of 1 cm was positioned in the coronary sinus for mapping of retrograde atrial activation sequence during induced tachycardia. Multiple surface electrocardiographic leads as well as intracardiac electrograms were recorded simultaneously on a multichannel oscilloscopic photographic recorder (Electronics for Medicine DR-16) at paper speeds of 100 and 200 mm/sec. Stimuli were provided by a programmable digital stimulator (manufactured by M. Bloom, Narbeth, Pennsylvania) with a strength of approximately twice diastolic threshold and a duration of 2 msec.

Electrophysiologic studies included the following[15–18]: (1) Incremental atrial pacing, (2) atrial extrastimulus testing at two or more cycle lengths, (3) incremental ventricular pacing, (4) ventricular extrastimulus testing at one or more cycle lengths, (5) mapping of retrograde atrial activation sequence during paroxysmal supraventricular tachycardia from multiple sites including low septal right atrium, coronary sinus (proximal, middle and distal), low lateral right atrium and high right atrium, and (6) atrial or ventricular extrastimulus testing, or both, during tachycardia. Retrograde stimulation studies were not performed in patients studied before 1973.

Statistical analysis: Clinical and electrocardiographic data among groups as a whole were analyzed statistically utilizing one way classification analysis of variance or multiple contingency tables. Individual groups were then compared with Student's *t* test or the chi square test.

Results

In 72 of the 79 patients, paroxysmal supraventricular tachycardia was reproduced in the cardiac catheterization laboratory, allowing delineation of the mechanism of the arrhythmia as described later. In seven patients, arrhythmia could not be reproduced, so that determination of a mechanism was impossible.

Electrophysiologic Characteristics

A-V nodal reentrant tachycardia: Fifty of the 72 patients (69 percent) had A-V nodal reentrant paroxysmal tachycardia diagnosed utilizing combinations of the following diagnostic criteria: (1) induction of tachycardia related to achievement of a critical A-H (atrio-His bundle) delay, with both incremental atrial pacing and atrial extrastimulus testing (48 patients)[3,15,17,19–21]; (2) demonstration of discontinuous A_1-A_2 and H_1-H_2 curves, suggesting dual A-V nodal pathways, with induction of tachycardia relating to anterograde block in the fast pathway (34 patients)[15,19–27]; (3) induction of tachycardia related to achievement of a critical V-A (ventriculoatrial) delay, during incremental ventricular pacing and with ventricular extrastimulus testing (seven patients)[15,17,28]; and (4) demonstration of discontinuous V_1-V_2, A_1-A_2 curves, suggesting retrograde dual A-V nodal pathways, with induction of tachycardia relating to retrograde block in the A-V nodal fast pathway (two patients).[28] Because criteria (1) and (2) could be fulfilled in patients with concealed extranodal pathways, one or more of the following additional criteria were required for the diagnosis of A-V nodal reentry: (5) demonstration of atrial activation before or simultaneous with onset of ventricular activation during tachycardia, suggesting that the ventricles were not a distal common pathway for reentrance (32 patients)[17]; (6) normal retrograde atrial activation sequence during tachycardia with the low septal right atrium being activated earlier than all other atrial recording sites (50 patients)[18,29]; (7) increase of V-A interval with incremental ventricular pacing with type I V-A block at a critical rate, suggesting retrograde A-V nodal conduction (16 patients)[15,17]; and (8) demonstration of His bundle activation (H_2) preceding the atrial activation (A_2) with ventricular extrastimulus testing during ventricular pacing or paroxysmal supraventricular tachycardia, or both, suggesting retrograde A-V nodal conduction (21 patients).[17]

Reentrance tachycardia utilizing a concealed extranodal pathway: Nine of the 72 patients (13 percent) had A-V reentrance utilizing a concealed extranodal pathway conducting in retrograde manner on the basis of combinations of the following criteria: (1) induction of tachycardia related to achievement of a critical A-V conduction time (nine patients),[4–8] (2) capture of the atria with a ventricular extrastimulus delivered during tachycardia when the His bundle was refractory (five patients),[4–8] (3) increase in V-A interval during tachycardia with functional bundle branch block ipsilateral to a concealed extranodal pathway (five patients),[5–8] (4) fixed V-A interval during incremental ventricular pacing (nine patients),[8,17,30] and (5) abnormal retrograde atrial activation sequence during tachycardia with the left atrium being activated before the low septal right atrium (nine patients).[8–16] With these criteria, all nine patients had evidence of a concealed left-sided extranodal pathway that participated in the supraventricular tachycardia. None of the nine

patients had discontinuous A_1-A_2 or H_1-H_2 curves. One of the nine patients manifested anterograde preexcitation only when the mid or distal coronary sinus was stimulated.

Sinus or atrial reentrance tachycardia: Seven of the 72 patients (10 percent) had sinus or atrial reentrance diagnosed utilizing combinations of the following diagnostic criteria: (1) Induction of tachycardia was related to achievement of critical atrial rates and critical A_1-A_2 coupling intervals.[9,10,31] (2) Induction of tachycardia was not related to achievement of critical A-H, A-V or V-A conduction time (seven patients).[10,31] (3) Induction of tachycardia occurred with ventricular stimulation (extrastimulus technique or incremental pacing) upon achievement of critical atrial coupling intervals (three patients). With this type of induction, the sequence of induction was $V_2 \rightarrow A_2 \rightarrow A_3$ (first beat of tachycardia). This was in contrast to induction of tachycardia from the ventricles with A-V nodal reentrance or A-V reentrance utilizing an anomalous pathway conducting in retrograde manner, where the sequence was $V_2 \rightarrow A_2 \rightarrow V_3$ (first beat of tachycardia).[10,31] (4) Induction of tachycardia occurred with initiating atrial stimuli that were blocked proximal to the His bundle recording site (five patients).[10,31] (5) Tachycardia was sustained despite A-V block proximal to the His bundle recording site (three patients).[10,31] (6) V-A conduction was absent, excluding concealed extranodal pathways and A-V nodal reentrance.[10,31,32] A diagnosis of sinus nodal reentrance was made when atrial activation sequence and P wave contour resembled those of sinus P waves (two patients).[10,31] A diagnosis of atrial reentrance was made when atrial activation sequence and P wave contour were different from those of sinus P waves (five patients).[10,31]

Automatic ectopic tachycardia: Three of the 72 patients (4 percent) had a diagnosis of automatic ectopic tachycardia (atrial focus in 1 and His bundle in 2). The criteria for diagnosis of automatic ectopic tachycardia included the following: (1) spontaneous onset of tachycardia not related to any initiating event, either critical rates or coupling intervals (three patients),[10,12,31] (2) spontaneous tachycardia during study with the initiating beat being identical to subsequent beats of tachycardia (three patients),[11,12,31] (3) inability to initiate and terminate the tachycardia with atrial and ventricular stimulations,[11,12,31] (4) demonstration of ectopic focus recovery time after cessation of overdrive pacing (three patients),[12,33] and (5) absence of dual A-V nodal pathways or concealed extranodal pathways (three patients).

Undefined mechanism of tachycardia: In 3 of the 72 patients (4 percent), differentiation between A-V nodal reentrance and reentrance utilizing a concealed extranodal pathway could not be made. In these three patients, induction of tachycardia was related to achievement of a critical A-H interval (not independent of a critical A-V interval). Because all had atrial activation occurring after ventricular activation during tachycardia and none had retrograde stimulation studies, the presence or absence of a concealed extranodal pathway could not be determined.

Selected Clinical Characteristics

Selected clinical characteristics were analyzed and compared in the three largest groups: those with A-V nodal reentrance, those with A-V reentrance utilizing concealed extranodal pathways, and those with sinoatrial reentrance.

Age and sex: The mean age (± standard error of the mean) was 55 ± 2 years (range 24 to 81) among patients with A-V nodal reentrance, 40 ± 6 years (range 12 to 69) among patients with concealed extranodal pathways and 49 ± 7 years (range 13 to 63) among patients with sinus or atrial reentrance. Patients with concealed extranodal pathways were significantly younger than those with A-V nodal reentrance ($P < 0.05$).

There was a male predominance in all three groups: There were 27 male (54 percent) and 23 female (46 percent) subjects with A-V nodal reentrance, 7 male (78 percent) and two female (22 percent) subjects with concealed extranodal pathway, and 4 male (57 percent) and 3 female subjects with sinus or atrial reentrance. The three groups were not significantly different in regard to sex.

Organic heart disease: The presence or absence of organic heart disease was diagnosed utilizing clinical, noninvasive and, if indicated, invasive cardiovascular studies (Fig. 1). Organic heart disease was diagnosed in 23 of 50 patients (46 percent) with A-V nodal reentrance, in 1 of the 9 patients (11 percent) with concealed extranodal pathways and in all 7 patients (100 percent) with sinus or atrial reentrance. The prevalence of organic heart disease in patients with concealed extra-

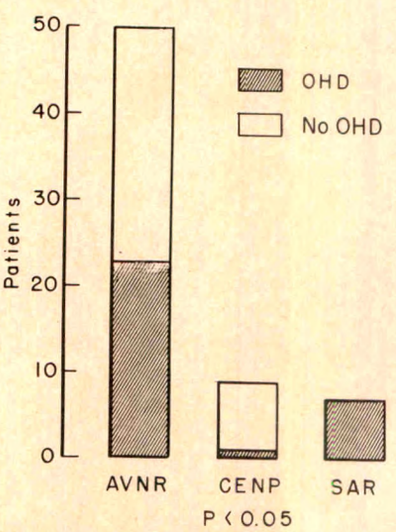


FIGURE 1. The presence or absence of organic heart disease (OHD) in the three groups of patients. The prevalence of organic heart disease in patients with a concealed extranodal pathway was significantly less than in those with A-V nodal and sinoatrial reentrance (P [probability] <0.05). AVNR = A-V nodal reentrance; CENP = A-V reentrance utilizing concealed extranodal pathways; SAR = sinoatrial reentrance.

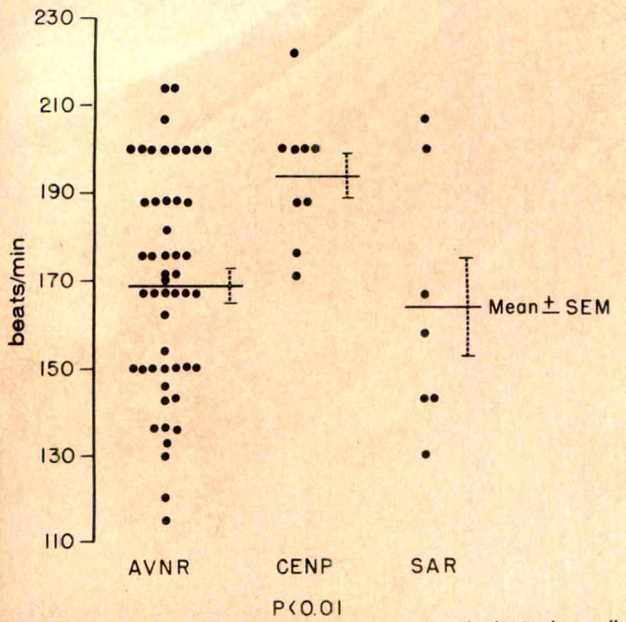


FIGURE 2. Heart rate during paroxysmal supraventricular tachycardia in three groups of patients. Each patient is represented by a **solid circle.** Paroxysmal supraventricular tachycardia in patients with a concealed extranodal pathway was significantly faster than in the other two groups (P [probability] <0.01). SEM = standard error of the mean; other abbreviations as in Figure 1.

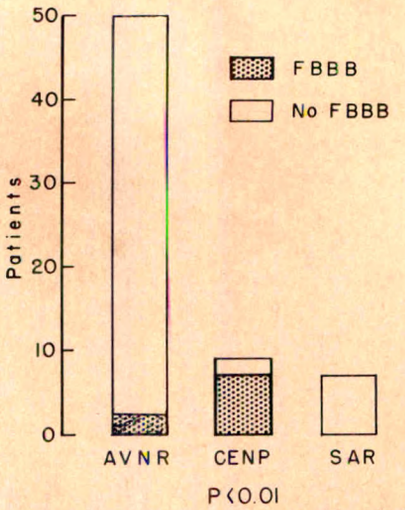


FIGURE 3. The presence or absence of functional bundle branch block (FBBB) during paroxysmal supraventricular tachycardia in the three groups of patients. The incidence of functional bundle branch block during tachycardia was significantly greater in patients with a concealed extranodal pathway (CENP) than in the other two groups (P [probability] <0.01). AVNR = A-V nodal reentrance; SAR = sinoatrial reentrance.

nodal pathways was significantly less than in patients with A-V nodal reentrance and sinoatrial reentrance ($P < 0.05$).

Selected Electrocardiographic Findings

Heart rate: Heart rates during spontaneous episodes of A-V nodal reentrant tachycardia ranged from 115 to 214/min (mean ± standard error 169 ± 4/min) (Fig. 2); during tachycardia in patients with concealed extranodal pathways it ranged from 171 to 222/min (mean 194 ± 5/min); and during sinus or atrial reentrance it ranged from 130 to 207/min (mean 164 ± 11/min). Paroxsymal supraventricular tachycardia in patients with a concealed extranodal pathway was significantly faster than in the other two groups ($P < 0.05$).

Functional bundle branch block: The presence or absence of functional bundle branch block during spontaneous episodes of paroxysmal supraventricular tachycardia was evaluated in the three groups (Fig. 3). Functional bundle branch block was observed in 2 of 50 patients (4 percent) with A-V nodal reentrant tachycardia, 7 of 9 patients (78 percent) with concealed extranodal pathways and none of 7 patients with sinus or atrial reentrance. The two patients with functional bundle branch block during A-V nodal reentrant tachycardia had right bundle branch block. Of the seven patients with concealed extranodal pathways, functional right bundle branch block alone was observed in two, functional left bundle branch block alone in two, and both functional right and left bundle branch block (on different occasions) in three. The incidence of functional bundle branch block during tachycardia in patients with concealed extranodal pathways was significantly greater than in those with A-V nodal reentrance and sinus or atrial reentrance ($P < 0.01$).

Timing of atrial activation relative to ventricular activation: This was evaluated during epixodes of paroxysmal supraventricular tachycardia. In many patients, there was observer disagreement as to whether P waves were seen and when they occurred. Because of this, recording of atrial electrograms (intraatrial or esophageal) during tachycardia episodes was utilized to delineate exactly the timing of atrial activation. The onset of the P wave was determined from the earliest site of atrial activation in the atrial electrograms. P waves were defined as occurring simultaneous with the QRS complex, after the QRS complex (if atrial activation was initiated after the termination of the QRS complex and before the mid point between the termination of one QRS complex and the onset of the next) or in front of the QRS complex (if atrial activation was initiated after the mid point) (Fig. 4 and 5). In the 50 patients with A-V nodal reentry, a retrograde P wave was simultaneous with the QRS complex in 33 (66 percent), after the QRS complex in 15 (30 percent) and before the QRS in 2 (4 percent). In all nine patients with A-V reentrance utilizing a concealed extranodal pathway, retrograde P waves occurred after the QRS complex. In six of the seven patients (85 percent) with sinus or atrial reentrance, the P wave occurred in front of the QRS complex and in one patient (15 percent) after the QRS complex.

In an attempt to predict the usefulness of timing of atrial activation during paroxysmal supraventricular tachycardia, we reversed our analysis. In 32 patients, atrium and ventricle were simultaneously activated during tachycardia. In all of these, paroxysmal supraventricular tachycardia was A-V nodal reentrant. In 25 patients, the P wave followed the QRS complex during

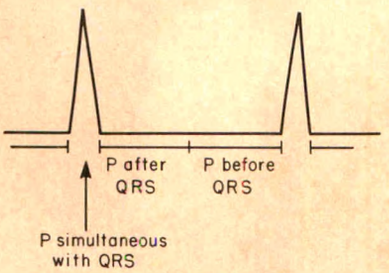


FIGURE 4. Diagrammatic representation of the timing of P waves relative to the QRS complex during paroxysmal supraventricular tachycardia (see text for discussion).

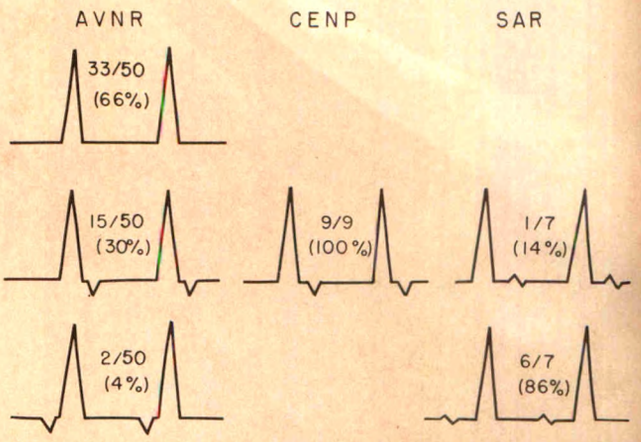


FIGURE 5. The timing of P waves relative to the QRS complex during paroxysmal supraventricular tachycardia in the three groups of patients. **Top panel,** P waves occurring simultaneously with the QRS complex. **Middle panel,** P waves after the QRS complex. **Lower panel,** P waves in front of the QRS complex (see text for discussion). Abbreviations as in Figure 1.

tachycardia. Fifteen of these 25 patients (60 percent) had A-V nodal reentrance, 9 (36 percent) had reentrance utilizing concealed extranodal pathways and one (4 percent) had sinoatrial reentrance. In eight patients the P wave occurred before the QRS complex during tachycardia. Of these eight, two (25 percent) had A-V nodal reentrance and six (75 percent) had sinoatrial reentrance.

Discussion

Our study demonstrated that in approximately 90 percent of patients with recurrent spontaneous paroxysmal supraventricular tachycardia, the arrhythmia could be reproduced in the cardiac catheterization laboratory. In addition, a specific mechanism could be defined in most of the patients with atrial and ventricular stimulation techniques. Atrioventricular (A-V) nodal reentrance was the most common mechanism defined, although other mechanisms when considered together were not infrequent. The latter mechanisms included reentrance utilizing concealed extranodal pathways, sinus or atrial reentrance and automatic atrial or His bundle tachycardia. In approximately 10 percent of patients, arrhythmias were not reproduced. Inability to reproduce arrhythmia in the latter group of patients could reflect an automatic mechanism or an unsuitable autonomic tone on the day of study.

Anatomic basis for sinoatrial and A-V nodal reentrant tachycardia: Several clinical and electrocardiographic features were associated with specific mechanisms of tachycardia. Organic heart disease was diagnosed in all patients with sinoatrial reentrant tachycardia, in approximately 50 percent of patients with A-V nodal reentrant tachycardia and in only 11 percent of patients with tachycardia reflecting reentrance utilizing a concealed extranodal pathway. These observations suggest an acquired anatomic basis for most sinoatrial reentrant tachycardia and for some A-V nodal reentrant tachycardia. In the case of sinoatrial reentrance, we postulate atrial stretch and fibrosis as factors predisposing to inhomogeneous conduction in the sinus node or atria, or both, facilitating the occurrence of sustained reentrance.[10,34] In regard to A-V nodal reentrance, we postulate that anatomic injury to the node with acquired organic heart disease predisposes to longitudinal dissociation of the A-V node.[22] The low prevalence rate of organic heart disease in patients with tachycardia due to concealed extranodal anomalous pathways is consistent with a congenital basis for this type of reentrance.

The ages associated with specific mechanisms of paroxysmal supraventricular tachycardia were generally consistent with the prevalence of organic heart disease associated with specific mechanisms as described. Patients with sinoatrial reentrance and A-V nodal reentrance were older than the patients with concealed extranodal anomalous pathways. However, there was considerable overlap in ages among the three large groups of patients with paroxysmal supraventricular tachycardia.

Rate of tachycardia and location and function of reentrant pathway: The heart rates observed during spontaneous episodes of tachycardia in the three groups appear to reflect the location and conducting characteristics of the tissues in which reentry occurred. In regard to sinus nodal or A-V nodal reentry, we envision a small dimension circus movement in slowly conducting perisinus nodal tissue (in the former case) and within the A-V node (in the latter case). In regard to atrial reentry, the location of intraatrial circus movements in man is not known. The resultant rates of spontaneous paroxysmal supraventricular tachycardia reflect the geometry and function of the tissues involved. In regard to reentrance utilizing concealed extranodal pathways, the circus movement reflects retrograde conduction in an anomalous pathway (relatively fast) and anterograde conduction in a healthy normal pathway, ventricle and atrium. Paroxysmal supraventricular tachycardia in patients with concealed extranodal pathways was generally faster than that occurring because of sinoatrial or A-V nodal reentrance. Again, there was a considerable overlap in observed rates of tachycardia with these three specific mechanisms.

Factors predisposing to functional bundle branch block: The cause of the predisposition to functional bundle branch block during paroxysmal

supraventricular tachycardia in patients with concealed extranodal pathways is not clear. Several factors can be considered. First, the rate of tachycardia in this group was faster than in the other groups and could be a predisposing factor. However, 24 of the patients with A-V nodal reentrant tachycardia had equivalently fast rates, with only 2 patients demonstrating functional bundle branch block during tachycardia. Second, the coupling interval of the initiating beat could be a determining factor. In patients with A-V nodal reentrant tachycardia, the initiating premature beat was usually associated with marked prolongation of A-V nodal conduction time, reflecting anterograde conduction through a slow A-V nodal pathway.[19–23] This would result in an initiating beat with a long H_1-H_2 coupling interval, longer than the refractory period of the bundle branches with a resultant narrow QRS complex. In patients with reentrance utilizing concealed extranodal pathways, the initiating premature beat was associated with a relatively short A-V nodal conduction time, with resulting H_1-H_2 coupling intervals that were shorter than the refractory periods of the bundle branches thus causing bundle branch block.[35] Once the initiating beat was blocked in one bundle, retrograde repetitive concealed conduction maintained the functional bundle branch block during tachycardia.[36,37] Third, it is possible that concealed extranodal pathways are associated with specific structural or functional abnormalities in the bundle branch system, not as yet described.

Timing of P waves and mechanism of tachycardia: The timing of P waves relative to the QRS complex during episodes of paroxysmal supraventricular tachycardia reflected the mechanism of tachycardia. In patients with concealed extranodal pathways conducting in retrograde fashion, the atria were activated after activation of the ventricular insertion of the extranodal pathway (which is a late ventricular activation site contiguous to the A-V ring).[18] Thus, P waves occurred after the QRS complex during episodes of tachycardia. In patients with sinus or atrial reentrance, anterograde A-V nodal conduction determined the relative timing of the P wave and QRS complex. P waves usually occurred in front of the QRS complex during episodes of tachycardia because atrial rates were relatively slow and A-V nodal conduction was not depressed. In patients with A-V nodal reentrance, atrial and ventricular activation were dependent upon the anterograde and retrograde conduction times of dual A-V nodal pathways. In the common type of A-V nodal reentrance, anterograde conduction is through a slow pathway and retrograde conduction through a fast pathway.[15,19–21,23] The relation of anterograde slow and retrograde fast pathway conduction times usually results in simultaneous atrial and ventricular activation. In some cases of this common type of A-V nodal reentrance, P waves occur after the QRS complex, reflecting slightly slower retrograde fast pathway conduction time. Much less commonly, A-V nodal reentrance reflected anterograde fast pathway and retrograde slow pathway conduction.[28] In these cases, retrograde P waves occurred in front of the QRS complex during tachycardia.

Clinical implications: In most patients with paroxysmal supraventricular tachycardia, the arrhythmia can be reproduced in the cardiac catheterization laboratory, allowing delineation of a mechanism of tachycardia. The most common mechanism of paroxysmal supraventricular tachycardia appears to be A-V nodal reentrance although other mechanisms are not infrequent. Typical findings suggestive of A-V nodal reentrant tachycardia include a narrow QRS complex and a P wave simultaneous with the QRS complex. Associated organic heart disease is not uncommon. A-V reentrant tachycardia reflecting concealed extranodal pathways is typically associated with young age, absence of organic heart disease, relatively fast rates, frequent occurrence of functional bundle branch block during tachycardia and P waves following the QRS complex. Sinus or atrial reentrance is characterized by a large prevalence of organic heart disease, a narrow QRS complex and P waves before the QRS complex. In our experience, the prediction of mechanisms can often be accomplished with clinical and electrocardiographic observation.

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Electrophysiologic Characteristics of Concealed Bypass Tracts: Clinical and Electrocardiographic Correlates

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Twelve of 60 consecutively studied patients undergoing electrophysiologic study for paroxysmal supraventricular tachycardia had atrioventricuar (A-V) bypass tracts functioning as the retrograde limb of the reentrant circuit. None had evidence of preexcitation in the surface electrocardiogram, but in two patients anterograde preexcitation could be produced by pacing from the coronary sinus. In all 12 patients with concealed bypass tracts the retrograde atrial activation sequence or effect of left bundle branch block aberration during the tachycardia, or both, confirmed the left-sided bypass tract. A negative P wave in lead I during the tachycardia was also diagnostic of a left-sided bypass tract. Dual A-V nodal pathways were found in five patients with concealed bypass tracts but were unrelated to the development of the tachycardia. When compared with supraventricular tachycardia due to A-V nodal reentry, clinical findings suggestive of a concealed bypass tract included: (1) P wave following the QRS complex (12 of 12 versus 12 of 40), (2) negative P wave in lead I during the tachycardia, and (3) bundle branch block aberration during the tachycardia (8 of 12 versus 3 of 40). Other characteristics of patients with concealed bypass tracts that were of less value in individual cases were shorter cycle lengths of tachycardia, younger patient age and lesser incidence of organic heart disease.

Intracardiac stimulation and recording techniques have led to the recognition that bypass tracts functionally silent during sinus rhythm, and therefore clinically unsuspected, are frequently responsible for cases of supraventricular tachycardia.[1–12] Recently several series of patients with supraventricular tachycardia utilizing such concealed bypass tracts have been described[9–12]; however, the clinical setting and electrocardiographic correlates have not been emphasized.

Material and Methods

Sixty patients with paroxysmal supraventricular tachycardia underwent electrophysiologic evaluation between January 1972 and August 1977. Patients were studied in the nonsedated postabsorptive state after informed consent was obtained. Antiarrhythmic drugs were withheld for 24 hours before each study.

Standard electrode catheters (1 cm interelectrode distance) were inserted percutaneously through femoral or antecubital veins, or both, and advanced under fluoroscopic control to positions in the right atrium, atrioventricular (A-V) junction to obtain a His bundle electrogram, right ventricle and, in 49 cases, the coronary sinus. When stimulation and recording were required from the same catheter a quadripolar electrode catheter was utilized with the proximal pair of electrodes used for recording and the distal pair of electrodes for stimulation. Stimulation was performed with a constant current source. Multiple intracardiac electrograms were simultaneously displayed with two or three surface electrocardiograms on a switch beam oscilloscope (Electronics for Medicine DR 16) and recorded on magnetic tape (Honeywell 5600C). Subsequently data were retrieved on photographic paper at speeds of 100 to 400 mm/sec.

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TABLE I

Patient Data

Case no.	Age (yr) & Sex	Cardiac Diagnosis
1	60 M	Cardiomyopathy
2	39 M	None
3	35 F	MVP
4	60 F	None
5	70 M	None
6	65 M	None
7	58 M	MVP
8	17 F	MVP
9	62 M	Old inf-post MI, CAD
10	63 F	MVP
11	25 M	None
12	18 F	None

CAD = coronary artery disease; Inf-post MI = inferoposterior myocardial infarction; MVP = mitral valve prolapse.

The following specific phenomena were evaluated to determine the mechanisms of supraventricular tachycardia: (1) the mode of initiation of the tachycardia with particular attention to site of conduction delay appearing requisite for the development of the arrhythmia; (2) the requirement of the atria or ventricles, or both, to initiate the tachycardia; (3) the atrial activation sequence and relation of the P wave to the QRS complex at the onset of and during the tachycardia; (4) the influence of bundle branch block, spontaneous or induced, on the cycle length and ventriculoatrial (V-A) conduction time during the tachycardia; and (5) the effect of atrial or ventricular stimulation, or both, during the tachycardia. Criteria used to diagnose supraventricular tachycardia using a concealed A-V bypass tract included: (1) initiation of the tachycardia in the absence of or not requiring a critical degree of A-V nodal conduction delay; (2) requirement of the ventricles to initiate and sustain the tachycardia; (3) abnormal retrograde atrial activation sequence during the tachycardia with the earliest onset of atrial activation following the QRS complex; (4) similar V-A intervals during the tachycardia and ventricular pacing at the same rate of the tachycardia; (5) prolongation of the cycle length and V-A conduction time during supraventricular tachycardia by the development of bundle branch block ipsilateral to the bypass tract; and (6) the ability to preexcite the atrium with ventricular premature depolarizations during the tachycardia without affecting the His bundle electrogram. This latter finding is of particular value in identifying patients with tachycardia utilizing a septal bypass tract; in such cases the retrograde activation sequence during supraventricular tachycardia is normal and bundle branch block does not influence the cycle length or V-A conduction.[6] Criteria used for A-V nodal reentry have been previously reported.[5]

Results

Twelve of the 60 patients (20 percent) met criteria for the presence of an atrioventricular (A-V) bypass tract functioning as a retrograde limb during supraventricular tachycardia (Table I). Four patients had echocardiographic and clinical evidence of mitral valve prolapse, six had no heart disease, and two had clinically significant organic heart disease.

In 2 of the 12 patients with concealed bypass tracts anterograde ventricular preexcitation could be demonstrated by atrial pacing from the coronary sinus near the atrial insertion of the bypass tract although no electrocardiographic evidence of preexcitation was noted during sinus rhythm. No evidence of anterograde ventricular preexcitation could be demonstrated in the remaining 10 patients with any method of atrial stimulation.

Mode of Initiation of Supraventricular Tachycardia

Programmed atrial and ventricular stimulation initiated supraventricular tachycardia in all patients. During anterograde stimulation, supraventricular tachycardia typically developed after some degree of

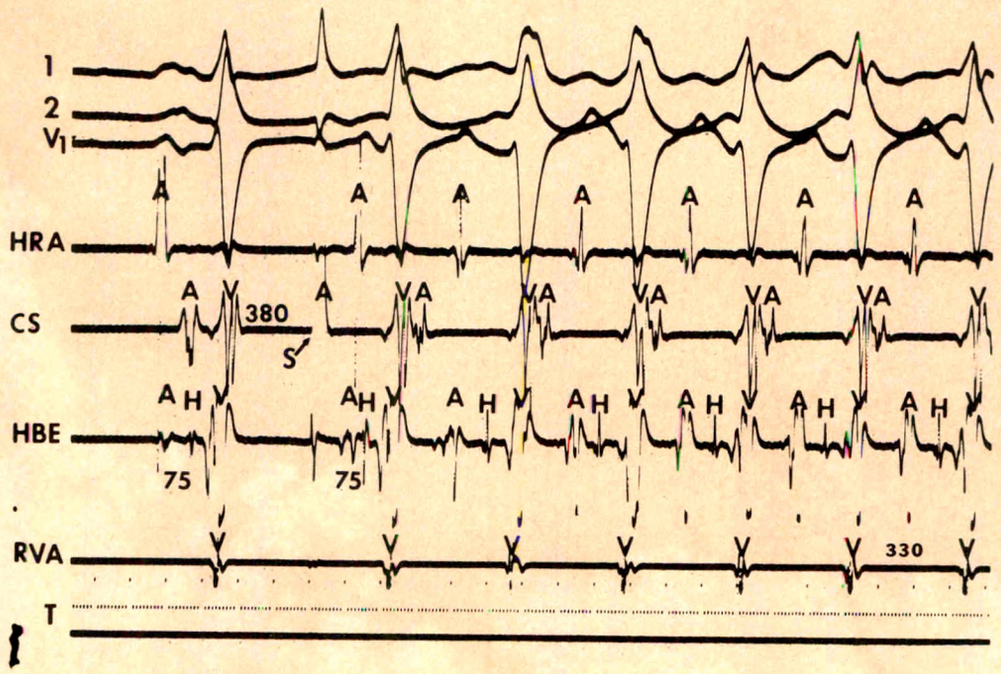


FIGURE 1. Case 1. Initiation of supraventricular tachycardia in the absence of A-V nodal delay. The figure is organized from **top to bottom** as follows: Electrocardiographic leads I (1), II (2) and V_1 and electrograms from the high right atrium (HRA), coronary sinus (CS), His bundle (HBE) and right ventricular apex (RVA) and time (T) scale. A, H and V = atrial, His bundle and ventricular electrograms, respectively. S = stimulus artifact. An atrial premature depolarization **(S, arrow)** delivered from the coronary sinus at a coupling interval of 380 msec results in supraventrcular tachycardia. The A-H interval of the sinus complex and the premature complex are identical. Note that the earliest retrograde activation during the tachycardia is recorded from the coronary sinus. See text for further discussion.

A-V delay was induced. In two patients, however, no A-V delay was required; the tachycardia occurred either with a spontaneous change in the cycle length or during relatively late atrial premature depolarizations delivered from the coronary sinus (Fig. 1). In one patient a His premature depolarization initiated supraventricular tachycardia.

In all patients supraventricular tachycardia could be initiated with rapid ventricular pacing or programmed ventricular stimulation, or both, in the absence of V-A conduction delay (Fig. 2). In each instance the V-A interval and the retrograde atrial activation sequence during ventricular stimulation were similar to those during the tachycardia. In seven patients ventricular premature depolarizations delivered at long coupling intervals (more than 75 percent of the paced cycle length) resulted in retrograde atrial activation over both pathways producing an atrial fusion complex.[13,14] When conduction proceeded solely over the bypass tract, supraventricular tachycardia was initiated. Thus, the initiation of supraventricular tachycardia during ventricular stimulation depended upon the development

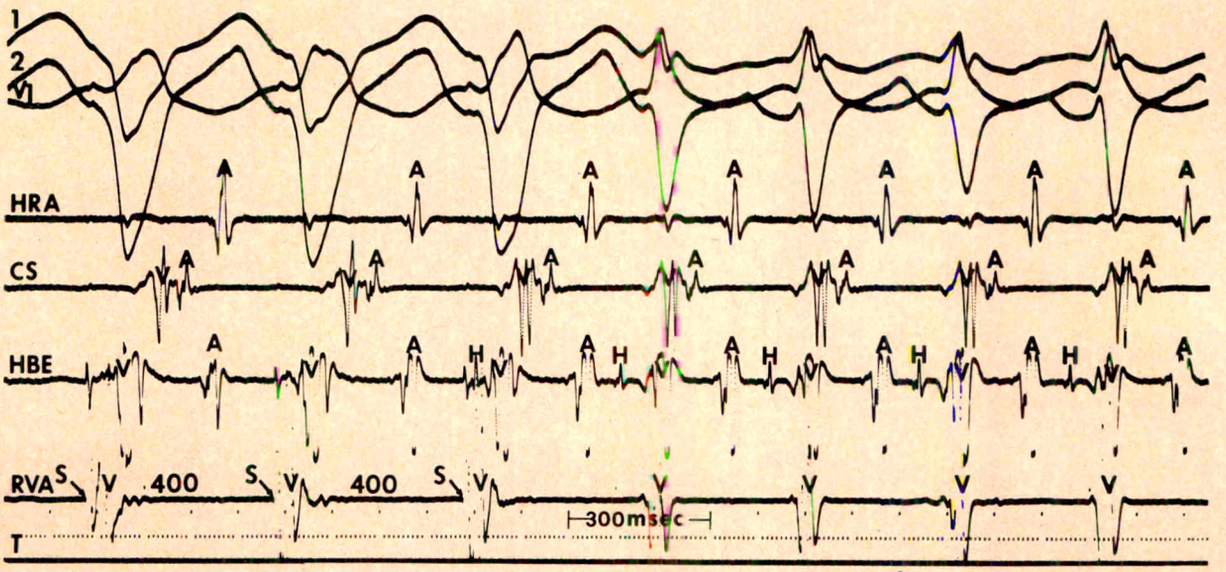


FIGURE 2. Case 1. Initiation of supraventricular tachycardia by ventricular pacing. Pacing from the right ventricular apex **(S, arrow)** at a cycle length of 400 msec initiates supraventricular tachycardia. Retrograde atrial activation during ventricular pacing and supraventricular tachycardia is the same. Abbreviations as in Figure 1.

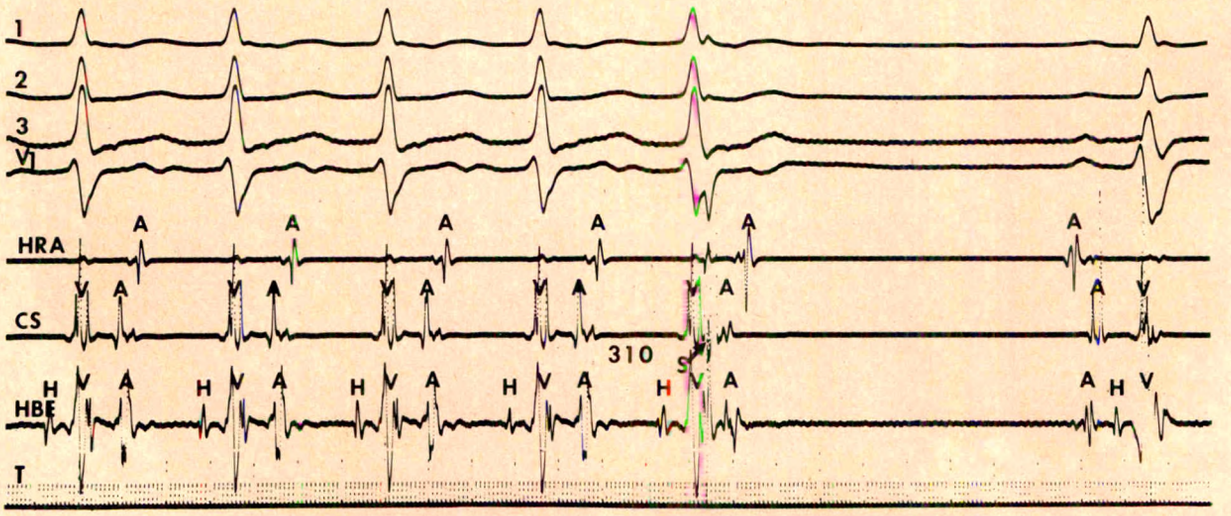


FIGURE 3. Case 3. Termination of supraventricular tachycardia by an atrial premature depolarization. Supraventricular tachycardia is present. After the fourth complex of supraventricular tachycardia, an atrial premature depolarization is introduced from the coronary sinus at a coupling interval of 310 msec **(S, arrow)**, which terminates the supraventricular tachycardia by creating atrioventricular nodal block. 3 = electrocardiographic lead III; other abbreviations as in Figure 1.

of retrograde block in the normal A-V conducting system.

Effects of Stimulation During Supraventricular Tachycardia

Rapid atrial or ventricular pacing (cycle lengths 250 to 500 msec) as well as programmed atrial or ventricular extrastimuli were able to terminate the tachycardia in each patient. In 10 patients termination was produced by A-V nodal block and was independent of the stimulation site, for example, atria or ventricles (Fig. 3). In contrast, in two cases termination of supraventricular tachycardia with ventricular premature depolarizations was produced with retrograde block in the bypass tract alone or simultaneously with retrograde block in the A-V node (Fig. 4).

In each of the 12 patients right ventricular stimulation during supraventricular tachycardia could preexcite the atria at a time when the His bundle was depolarized and therefore refractory (Fig. 5). In no instance was left ventricular stimulation necessary to demonstrate this phenomenon.

In two patients spontaneous termination was observed and resulted from progressive conduction delay and then block in the A-V node. Thus, as with termination of supraventricular tachycardia by programmed stimulation, spontaneous termination resulted from block in the anterograde limb of the reentrant circuit, that is, the A-V node. V-A conduction never changed during supraventricular tachycardia despite variations in A-V conduction produced with atrial stimulation.

Electrophysiologic Findings During Supraventricular Tachycardia

P wave configuration and atrial activation: In each of the 12 patients with concealed bypass tracts the

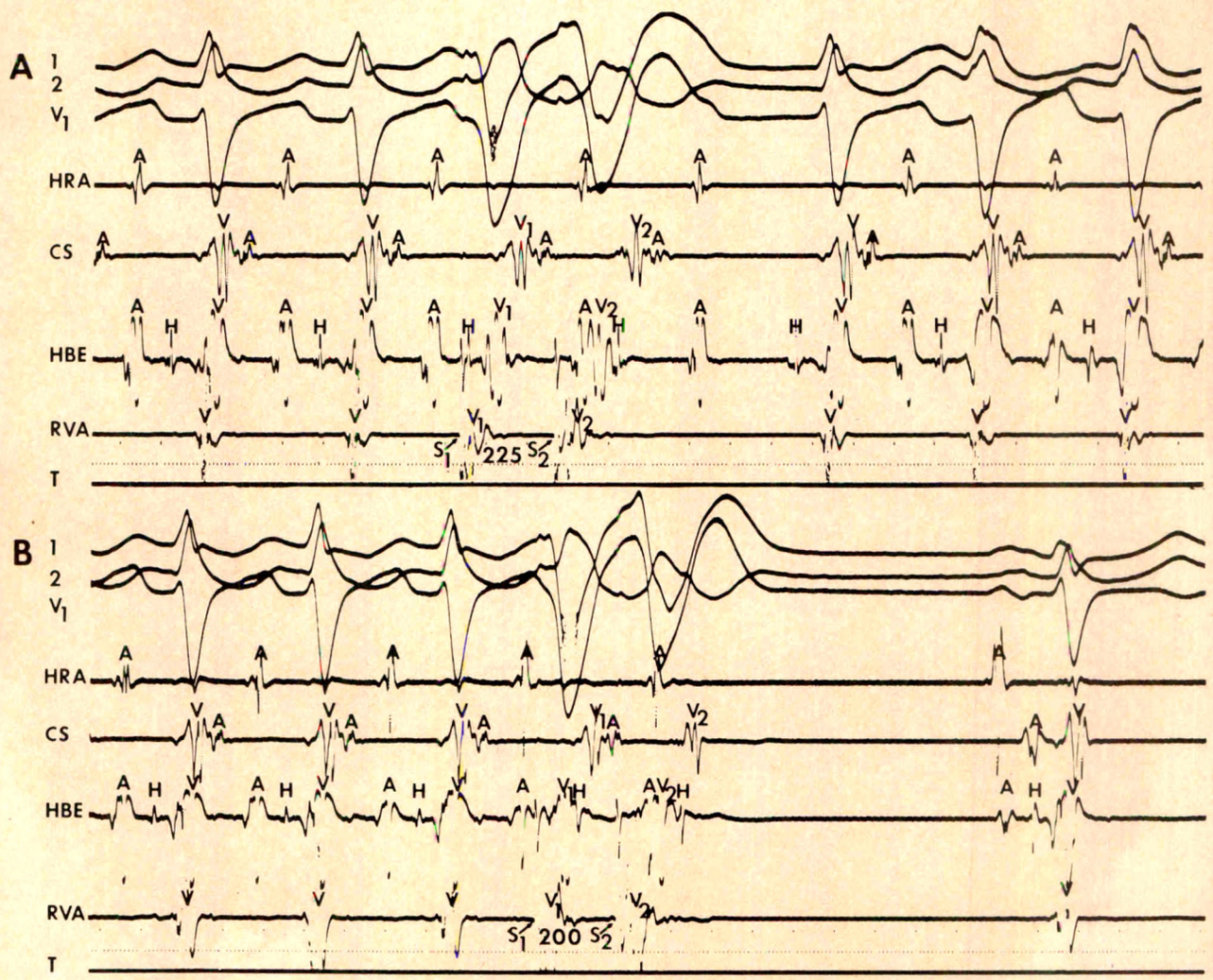


FIGURE 4. Case 1. Termination of supraventricular tachycardia by block in both normal and accessory atrioventricular (A-V) pathways in response to ventricular premature depolarizations. **A,** two ventricular premature depolarizations capture the atrium without interrupting anterograde conduction over the normal A-V conduction system. The second ventricular premature depolarization (S_2) preexcites the atrium early enough to produce prolongation of A-V nodal conduction. **B,** the second ventricular premature depolarization (S_2) terminates the tachycardia by blocking in both normal and accessory A-V pathways. Abbreviations as in Figure 1.

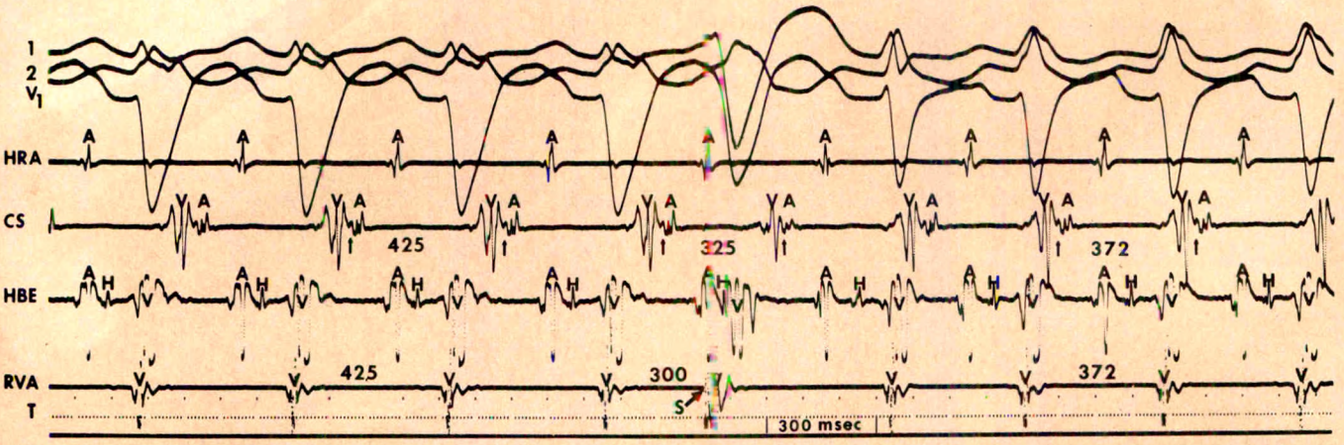


FIGURE 5. Case 1. Retrograde atrial preexcitation and normalization of the QRS complex by a ventricular premature depolarization during supraventricular tachycardia. During supraventricular tachycardia with left bundle branch aberration, a ventricular premature depolarization is introduced in the right ventricular apex **(S, arrow)** and conducts in retrograde fashion to the atrium after the His bundle has been depolarized in anterograde manner. This also results in normalization of the QRS complex with concomitant shortening of ventriculoatrial conduction time and cycle length (from 425 to 372 msec). Abbreviations as in Figure 1.

P wave was negative in lead I of the surface electrocardiogram during supraventricular tachycardia (Fig. 6, Table II), a finding that is considered diagnostic of left atrial orgin of atrial depolarization.[15–18] In each of the patients atrial depolarization (the earliest intracardiac or surface electrocardiographic recording) appeared shortly after the QRS complex with an R-P/R-R ratio of less than 0.5 (Table II). The earliest onset of retrograde atrial activation was recorded in the coronary sinus.

Functional bundle branch block during supraventricular tachycardia: Eight patients manifested bundle branch block during supraventricular tachycardia: seven at the onset and one during the arrhythmia. Five had aberration of both the left and right bundle branch block type. The cycle length and V-A conduction time during supraventricular tachycardia with left bundle branch block were longer than during supraventricular tachycardia with a normal QRS complex or with right bundle branch block (Table II). In patients manifesting functional bundle branch block at the initiation of the tachycardia, the presence and type of bundle branch block depended on the H_1-H_2 interval preceding the onset of the arrhythmia. In three patients with continuing bundle branch block during the tachycardia, ventricular premature depolarizations or ventricular pacing were able to normalize the QRS complex, allowing analysis of the effect of the bundle branch block on V-A conduction (Fig. 5). H-V prolongation was associated with the development of left

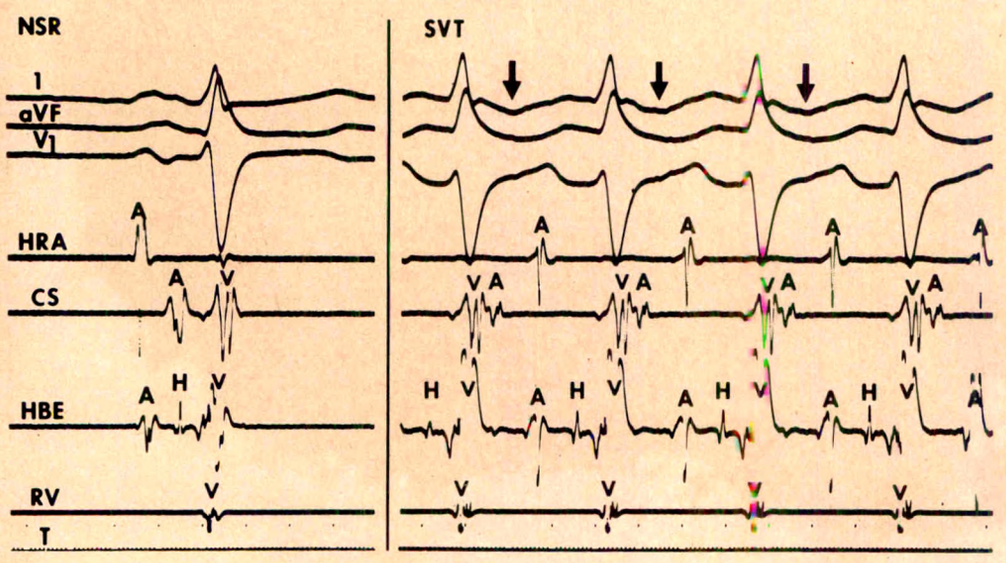


FIGURE 6. P wave configuration during supraventricular tachycardia with left-sided atrioventricular bypass tracts. During supraventricular tachycardia (SVT) negative P waves are seen in lead I **(arrows)** after the QRS complex in a patient with a left-sided bypass tract. aVF = electrocardiographic lead aVF; NSR = normal sinus rhythm; other abbreviations as in Figure 1.

bundle branch block in four of six patients and contributed to the prolongation of the cycle lengths of the tachycardia.

Associated A-V nodal dual pathways: In five patients (Cases 1, 6, 8, 10 and 12) dual A-V nodal pathways were demonstrated. In three (Cases 1, 6 and 8) the slow A-V nodal pathway functioned as the anterograde limb during supraventricular tachycardia, whereas in Patients 10 and 11 the fast pathway was utilized as the anterograde limb of the reentrant circuit.[19,20] A second, slow A-V nodal pathway was also demonstrated during supraventricular tachycardia when atrial or ventricular premature depolarizations, which were blocked in the fast pathway, conducted in anterograde fashion (Fig. 7).

Associated arrhythmias: In 6 of the 12 patients with concealed retrograde bypass tracts, rapid atrial or ventricular pacing, or both, during supraventricular tachycardia induced sustained atrial flutter or fibrillation, or both. In each case the flutter or fibrillation spontaneously converted to the supraventricular tachycardia or sinus rhythm.

Concealed Bypass Tract Versus A-V Nodal Reentry

The characteristics of supraventricular tachycardia utilizing the concealed bypass tract (12 patients) were compared with those of supraventricular tachycardia due to A-V nodal reentry (40 patients) (Table III). The remaining eight patients had sinus nodal reentry (five patients) or intraatrial reentry (three patients).

The following electrocardiographic features appeared to characterize supraventricular tachycardia utilizing a concealed bypass tract (Table III): (1) Rapid rate of supraventricular tachycardia. The average cycle length of supraventricular tachycardia was 337 ± 32 (mean ± standard error of the mean) msec and that due to A-V nodal reentry was 395 ± 25 msec. (2) The P wave followed the QRS complex with an R-P/R-R ratio less than or equal to 0.5 in all patients with supraventricular tachycardia using a concealed bypass tract whereas it did so in only 12 of 40 patients (30 percent) with A-V nodal reentry. (3) A negative P wave in lead I during supraventricular tachycardia was seen in all patients in which the arrhythmia utilized a retrograde concealed bypass tract but was not seen in any patient with A-V nodal reentry. (4) The incidence of functional bundle branch block was significantly greater in patients with supraventricular tachycardia utilizing a concealed bypass tract than in those with tachycardia secondary to A-V nodal reentry (8 of 12 versus 4 of 40). (5) There was a much greater incidence of induced atrial flutter or fibrillation in patients with concealed bypass (6 of 12 versus 1 of 40). Although differences existed in age, sex and the incidence of organic heart disease, too much overlap existed to make any of these variables useful in a differential diagnosis of the mechanism of

TABLE III

Comparison of Supraventricular Tachycardia Utilizing Concealed Bypass Tracts With A-V Nodal Reentrant Tachycardia

	SVT-CBT	SVT-AVNR
Average tachycardia cycle length (msec)	337 ± 32*†	385 ± 25†
Negative P wave in ECG lead I	12 of 12 (100%)*	0 of 40 (0%)
P wave following QRS	12 of 12 (100%)*	12 of 40 (30%)
Functional bundle branch block	8 of 12 (66%)*	3 of 40 (8%)
Induced atrial fibrillation	6 of 12 (50%)*	1 of 40 (2%)
Patients' age (yr)	48 ± 20†	59 ± 19†
Male/female ratio	2/1	1.5/1
Organic heart disease	2 of 12*	13 of 40

* $P < 0.05$.
† Mean ± standard error of the mean.
A-V = atrioventricular; ECG = electrocardiographic; SVT-AVNR = supraventricular tachycardia due to A-V nodal reentry; SVT-CBT = supraventricular tachycardia utilizing a concealed bypass tract.

TABLE II

Electrophysiologic Data on 12 Patients With Supraventricular Tachycardia Utilizing Concealed Bypass Tracts

Case no.	Cycle Length of SVT (msec)			R-P (msec)	P Wave ECG lead I	Early LA	AVN-FRP (msec)	Dual A-V Nodal Pathways	
	Normal QRS	With LBBB	With RBBB					Fast Pathway (anterograde)	Slow Pathway (anterograde)
1	330	420	310	110	Negative	+	370	+	−
2	300	355	300	120	Negative	+	310	+	−
3	350	370	340	120	Negative	+	350	. . .	. . .
4	260	−	260	100	Negative	+	290	. . .	. . .
5	330	380	330	100	Negative	+	370	. . .	. . .
6	370	410	370	70	Negative	+	370	. . .	. . .
7	335	−	−	110	Negative	+	400	−	+
8	340	−	345 +LAHB	100	Negative	+	335	−	+
9	350	400	−	120	Negative	+	340	−	+
10	340	−	−	110	Negative	+	310	. . .	. . .
11	380	−	−	90	Negative	+	350	. . .	. . .
12	360	−	−	100	Negative	+	360	. . .	. . .

+ = present; − = absent; . . . = not recorded.
A-V = atrioventricular; AVN-FRP = atrioventricular nodal functional refractory period; early LA = atrial depolarization noted first in coronary sinus (left atrial) electrode; ECG = electrocardiogram; LAHB = left anterior hemiblock; LBBB = left bundle branch block; RBBB = right bundle branch block; SVT = supraventricular tachycardia.

supraventricular tachycardia. The mean A-H intervals and functional refractory period of the A-V node in patients with supraventricular tachycardia utilizing a concealed bypass tract were shorter than those in a normal population (95 and 420 msec, respectively).[21,22]

Discussion

Incidence and clinical features: The use of programmed stimulation and endocardial mapping has provided evidence of multiple mechanisms for the arrhythmia termed paroxysmal supraventricular tachycardia.[23–25] In a suprisingly high proportion (20 percent) of patients with clinical supraventricular tachycardia and no manifestation of preexcitation in the surface electrocardiogram an atrioventricular bypass tract was utilized as the retrograde limb during the tachycardia. These patients are younger and have a lesser incidence of clinically significant heart disease than patients with A-V nodal reentrant supraventricular tachycardia.

Electrocardiographic correlates: Several electrocardiographic and clinical features distinguish patients with supraventricular tachycardia utilizing a concealed bypass tract. These may be helpful in the differential diagnosis of supraventricular tachycardia. In contrast to most patients with A-V nodal reentry tachycardia all patients with supraventricular tachycardia utilizing a concealed bypass tract demonstrated retrograde P waves. Moreover, these P waves were negative in lead I, a diagnostic feature of left-sided by-

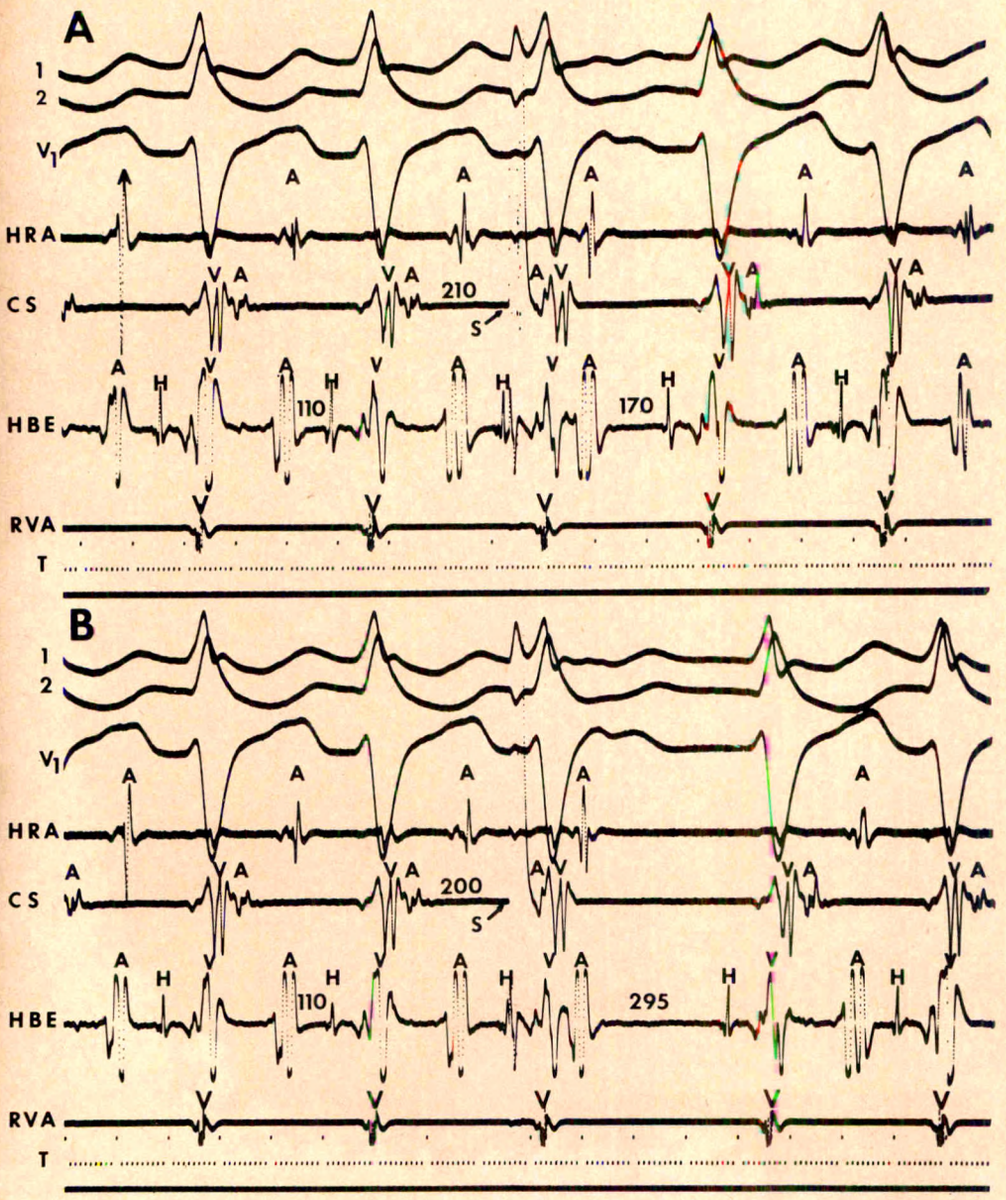


FIGURE 7. Demonstration of dual atrioventricular (A-V) nodal pathways during supraventricular tachycardia. **A,** an atrial premature depolarization (S) delivered in the coronary sinus (CS) at a coupling interval of 210 msec prolongs the A-H interval from 110 msec to 170 msec. **B,** an atrial premature depolarization (S) delivered at a slightly shorter coupling interval (200 msec) prolongs the A-H interval to 295 msec, suggesting block in a fast A-V nodal pathway and anterograde conduction through a slow A-V nodal pathway. The fast A-V nodal pathway is utilized as the anterograde limb of the tachycardia, and retrograde conduction occurs over the left A-V bypass tract. See text for further discussion. Abbreviations as in Figure 1.

pass tracts. Confirmation of this clinical clue was provided by endocardial atrial mapping, which demonstrated a left-sided bypass tract in all of our patients.

The average rate of supraventricular tachycardia incorporating a concealed bypass tract is faster than that of A-V nodal reentry tachycardia despite the longer reentry circuit in the former. Functional bundle branch block during the tachycardia is also very common in these patients. Both the rapid rate and large incidence of bundle branch block in patients with tachycardia using bypass tracts have a common explanation. We believe that both are related to relatively enhanced A-V nodal conduction and a short functional refractory period of the A-V node, which allows the His-Purkinje system to be engaged at shorter H_1-H_2 intervals than in normal subjects and specifically shorter intervals than in patients with A-V nodal reentry tachycardia. The functional refractory period of the A-V node allows the impulse to encounter a partially refractory bundle branch, producing the electrocardiographic abnormality. This does not happen in patients with A-V nodal reentry because most have dual A-V nodal pathways and the tachycardia is initiated only after a "jump" in H_1-H_2 intervals as conduction proceeds along the slow pathway[19,20,23,24]; therefore the relative refractory period of the His-Purkinje system is never encroached upon. The relative refractory periods of the His-Purkinje system in patients with concealed bypass tracts fall within the normal limits previously noted.[21] We therefore believe that both the rapid rate of the tachycardia and functional bundle branch block are the result of a shortened A-V nodal functional refractory period.

As noted by previous authors,[1–8] the presence of functional bundle branch block ipsilateral to the site of the bypass tract (in this case left bundle branch block) provides information important to making the diagnosis of an accessory pathway. During left bundle branch block the cycle length of the tachycardia and, more specifically, V-A conduction time during the tachycardia are prolonged. The explanation of this phenomenon is that the left bundle branch block necessitates that the impulse first pass through the right ventricle and then slowly by muscle conduction reach the ventricular end of the bypass tract in the left ventricle before retrograde conduction, and hence circus movement tachycardia, can ensue. Thus, the reentry circuit is lengthened and the conduction time within the ventricular component of the circuit is prolonged. As noted by Spurrell[26] and Wellens[5] and their co-workers, ventricular stimulation during supraventricular tachycardia can induce or abolish the bundle branch block enabling the investigator to analyze the effects of the block on the tachycardia. This procedure was useful in three of our patients.

Although delayed anterograde input to the A-V bypass tract might explain the normal P-R interval and QRS pattern in the surface electrocardiogram in patients with left-sided bypass tracts, unidirectional block was demonstrated in 10 of our 12 patients by atrial pacing at the site of the bypass tract. It is unclear why all concealed bypass tracts in our series and most previously reported are left-sided.[1–9]

Implications: The recognition of supraventricular tachycardia associated with concealed A-V bypass tracts is suggested by rapid heart rate, presence of functional bundle branch block and a discrete P wave following the QRS complex by an interval less than half the R-R interval. The observation of a negative P wave in lead I is virtually diagnostic of this type of supraventricular tachycardia. As newer specific antiarrhythmic drugs become available and the place of surgical therapy of refractory supraventricular tachycardia becomes established, the diagnosis of supraventricular tachycardia utilizing a concealed bypass tract assumes even greater significance.

Acknowledgment

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Effects of Propranolol on Anomalous Pathway Refractoriness and Circus Movement Tachycardias in Patients With Preexcitation

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Electrophysiologic effects of intravenous propranolol, 0.1 mg/kg, were evaluated in 18 patients with anomalous pathways utilizing intracardiac stimulation and recording. Fourteen patients had Wolff-Parkinson-White syndrome and four had concealed ventricular preexcitation. Anomalous pathway effective refractory period could be measured during the control period and after propranolol administration in nine patients and was 304 ± 7.5 (mean ± standard error of the mean) and 304 ± 8.3 msec, respectively (difference not significant). Ventricular paced 1:1 ventriculoatrial (V-A) conduction (reflecting retrograde anomalous pathway conduction) measured in 12 patients was intact during both the control period and after propranolol at rates of 170 to 200/min. Sustained paroxysmal supraventricular tachycardia was induced in 14 patients during the control period and in 10 after propranolol (in 4 of whom the tachycardia could not be sustained because of atrioventricular [A-V] nodal refractoriness). Mean cycle length of tachycardia in these 10 patients was 328 ± 18 (control) and 352 ± 19 msec (propranolol) ($P < 0.01$). The increase in tachycardia cycle length reflected an increase in A-V nodal conduction time (A-H interval).

In conclusion: (1) Propranolol has an insignificant effect on both anterograde and retrograde anomalous pathway properties. (2) In most cases, propranolol does not interfere with induction of sustained circus movement tachycardia. However, it does produce a statistically significant but slight slowing of the rate of tachycardia. (3) In a minority of cases, propranolol inhibits induction of sustained paroxysmal supraventricular tachycardia by increasing A-V nodal refractoriness.

Propranolol is frequently recommended for management of tachycardias complicating the Wolff-Parkinson-White syndrome.[1] Despite its frequent use in patients with preexcitation, little information is available regarding its electrophysiological effects on anomalous pathway properties and circus movement tachycardia. In 1972, on the basis of limited data, we[2] suggested that propranolol had a minimal effect on anomalous pathway refractoriness.[2] Preliminary studies by Morgan et al.[3] and Jengo et al.[4] confirmed these results and also noted the lack of effects of propranolol on cycle length of induced paroxysmal tachycardia.

In this study, we extend our previous observations by examining the effects of propranolol on anterograde and retrograde anomalous pathway properties and upon the induction and maintenance of circus movement tachycardias in patients with preexcitation.

Materials and Methods

Patient selection (Table I): Eighteen patients with anomalous extranodal atrioventricular (A-V) pathways were studied, their ages ranging from 12 to 62 years; 14 were male and 4 female. Fourteen patients had electrocardiograms demonstrating typical preexcitation (left-sided in seven and right-sided in seven). Localization of the anomalous pathway was performed as previously described

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TABLE I

Selected Electrophysiologic Findings in 18 Patients

Case no.	Type of Preexcitation	Max VR With 1:1 V-A Conduction (beats/min)		Ability to Induce Sustained PSVT		PSVT Cycle Length (msec)		PSVT A-H/H-A (msec)	
		C	P	C	P	C	P	C	P
1	B	200	200	No	No	—	—	—	—
2	A	200	200	Yes	Yes	270	320	120/150	170/150
3	B	200	200	Yes	No	300	—	150/150	—
4	A	200	200	Yes	Yes	370	390	200/170	220/170
5	B	—	—	No	No	—	—	—	—
6	A	—	—	Yes	Yes	290	300	120/170	130/170
7	A	—	—	No	No	—	—	—	—
8	A	—	—	Yes	Yes	270	300	130/140	160/140
9	B	170	180	Yes	Yes	440	490	270/170	315/175
10	B	170	170	Yes	No	480	—	280/190	—
11	B	200	200	Yes	Yes	320	340	130/190	150/190
12	A	180 (VAB)	180 (VAB)	Yes	Yes	340	340	180/160	180/160
13	B	200	200	Yes	Yes	280	320	110/170	150/170
14	A	200	200	No	No	—	—	—	—
15	CKB	180	180	Yes	Yes	340	350	190/150	200/150
16	CKB	200	200	Yes	No	310	—	170/140	—
17	CKB	—	—	Yes	No	380	—	190/190	—
18	CKB	190	190	Yes	Yes	350	370	170/180	190/180

C = control period; CKB = concealed Kent bundle; Max VR = maximal ventricular paced rate; P = propranolol; PSVT = paroxysmal supraventricular tachycardia; V-A = ventriculoatrial; VAB = ventriculoatrial block.

utilizing QRS configuration during maximal preexcitation, atrial pacing at multiple sites and atrial mapping during retrograde anomalous pathway conduction.[5–7] Four patients had no anterograde preexcitation, but did have concealed (conducted retrograde) left-sided anomalous A-V connections.[8–11] Eleven patients had previously documented recurrent paroxysmal supraventricular tachycardia, two had recurrent paroxysmal atrial fibrillation and five had recurrent paroxysmal palpitation without previously documented arrhythmia.

Electrophysiologic studies: Informed consent was obtained before electrophysiologic study. His bundle electrograms were recorded using a bipolar electrode catheter introduced percutaneously and placed at the tricuspid valve.[12] A hexapolar catheter, introduced through a right antecubital vein, was advanced to the right ventricular apex. The distal two electrodes were utilized for right ventricular pacing; the proximal four electrodes were positioned against the right lateral atrial wall and were used for high and mid right atrial recording and stimulation. A third quadripolar catheter, introduced through a left antecubital vein, was used for recording and stimulation from the coronary sinus. Electrocardiographic leads I, II, III and V_1, as well as atrial and His bundle electrograms, were simultaneously recorded on a multichannel oscilloscopic recorder (Electronics for Medicine, DR-16, White Plains, New York) at paper speeds of 100 and 200 mm/sec.

Stimuli were provided by a programmable digital pulse generator (manufactured by M. Bloom, Philadelphia) and were 2 msec in duration and approximately twice diastolic threshold. Incremental atrial pacing was performed in increments of 10 beats/min until one or more of the following was achieved: (1) a maximal atrial paced rate of 200/min; (2) induction of paroxysmal supraventricular tachycardia, and (3) A-V nodal Wenckebach periodicity. Anterograde refractory periods and echo zones were determined with the atrial extrastimulus technique, with test stimuli (S_2) introduced after every eighth driven or spontaneous sinus beat.[13–15]

Anomalous pathway retrograde properties were studied utilizing response to incremental ventricular pacing and the ventricular extrastimulus technique. Retrograde anomalous pathway conduction during supraventricular tachycardia was proved in all cases (both left- and right-sided anomalous connections) by one or more of the following criteria: (1) abnormal retrograde activation sequence[6,7,16]; (2) ability to capture the atria during supraventricular tachycardia with critically timed ventricular extrastimuli delivered when the His bundle was refractory[17]; and (3) increase in ventriculoatrial (V-A) conduction time during supraventricular tachycardia with development of bundle branch block ipsilateral to the anomalous pathway.[18] The presence of retrograde anomalous pathway conduction during incremental ventricular pacing was suggested by demonstration of one or more of the following criteria: (1) abnormal retrograde atrial activation sequence (early activation of atrium contiguous to the mid or lateral coronary sinus) detected in patients with left-sided anomalous pathways (9 patients)[6]; (2) induction of supraventricular tachycardia with incremental ventricular pacing, not related to a critical V-A interval, suggesting induction through block in the normal pathway (six patients with left-sided anomalous pathways and two patients with right-sided anomalous pathways)[19]; (3) fixed V-A conduction time during incremental ventricular pacing (18 patients),[16] and (4) retrograde activation sequence during incremental pacing identical to that observed during induced paroxysmal supraventricular tachycardia or A-V reentrant atrial echoes (18 patients). The possibility of rapid retrograde A-V nodal conduction during ventricular pacing was not absolutely excluded in five patients with right-sided pathways.

The ventricles were paced at rates slightly above sinus rate and then in increments of 10 beats/min until one of the following was achieved: (1) a maximal paced rate of 170 to 220/min (depending on clinical status of the patient); (2) induction of paroxysmal supraventricular tachycardia; and (3) development of ventriculoatrial block. Pacing was not performed at cycle lengths short enough to lose ventricular capture.

The occurrence of intact retrograde anomalous pathway conduction at short paced ventricular cycle lengths implied that anomalous pathway refractoriness was short enough to

allow retrograde participation in A-V reentrant supraventricular tachycardia. The retrograde refractory period of the anomalous pathway was defined as the longest ventricular coupling interval (V_1-V_2) at which V_2 failed to conduct to the atria through the anomalous pathway.[16] Ventricular pacing was performed from the right ventricular apex.

The ability to induce and sustain paroxysmal supraventricular tachycardia as well as the cycle length of induced tachycardia were noted. All of these measurements were completed before drug administration. Repeat measurements were initiated 10 minutes after administration of 0.1 mg/kg intravenous propranolol.[3,4,14]

Definitions: *Anomalous pathway anterograde effective refractory periods* were measured at identical atrial driven cycle lengths in seven patients before and after propranolol (cycle length range of 545 to 670 msec; mean ± standard deviation 602 ± 36) and were defined as the longest atrial coupling interval at which block was achieved in the anomalous pathway. In two patients, anomalous pathway refractory periods were measured during sinus rhythm (the respective sinus cycle lengths were 620 and 910 msec before and 650 and 970 msec after propranolol). Anomalous pathway refractory periods were measured from the same site before and after drug administration. This site was close to the anomalous pathway location in most of the patients.[5]

Anomalous pathway retrograde effective refractory periods were measured at an identical ventricular paced cycle length in 16 patients before and after propranolol (cycle length range 400 to 670 msec; mean ± standard deviation 565 ± 65 msec). In one patient the anomalous pathway retrograde refractory period was measured during sinus rhythm (cycle length 870 msec). In one patient anomalous pathway retrograde refractory period was not measured after propranolol administration.

Paroxysmal supraventricular tachycardia was defined (for the purpose of this study) as A-V reentrant tachycardia utilizing the normal pathway for anterograde conduction and the anomalous pathway for retrograde conduction.

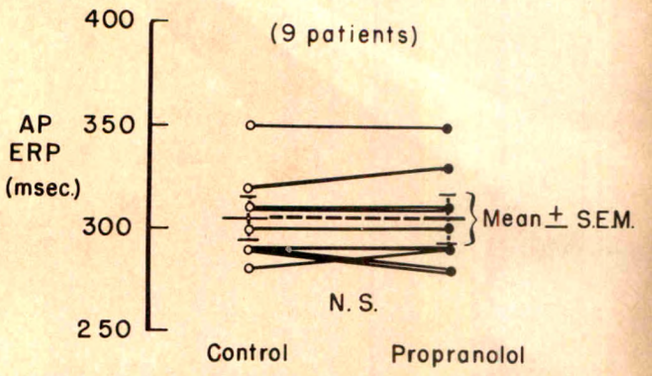


FIGURE 1. The effects of propranolol on anomalous pathway (AP) anterograde effective refractory periods (ERP). Control values are shown on the left, postpropranolol values on the right. Mean values ± standard error of the mean (S.E.M.) are also designated. N.S. = difference not significant.

Atrial echo zones were defined by the longest (outer limit) and shortest (inner limit) A_1-A_2 coupling intervals that resulted in induction of single echoes or repetitive reentrance. Paroxysmal supraventricular tachycardia was defined as sustained if it lasted 30 seconds or more, usually necessitating atrial or ventricular stimulation for termination. In most cases of nonsustained tachycardia, only single or double atrial echoes were observed.

Results

Anomalous pathway anterograde and retrograde properties: *Anomalous pathway anterograde effective refractory period* could be measured in 9 of the 14 patients with manifest preexcitation before and after propranolol (Fig. 1). (In three patients, intermittent preexcitation during the study precluded reliable

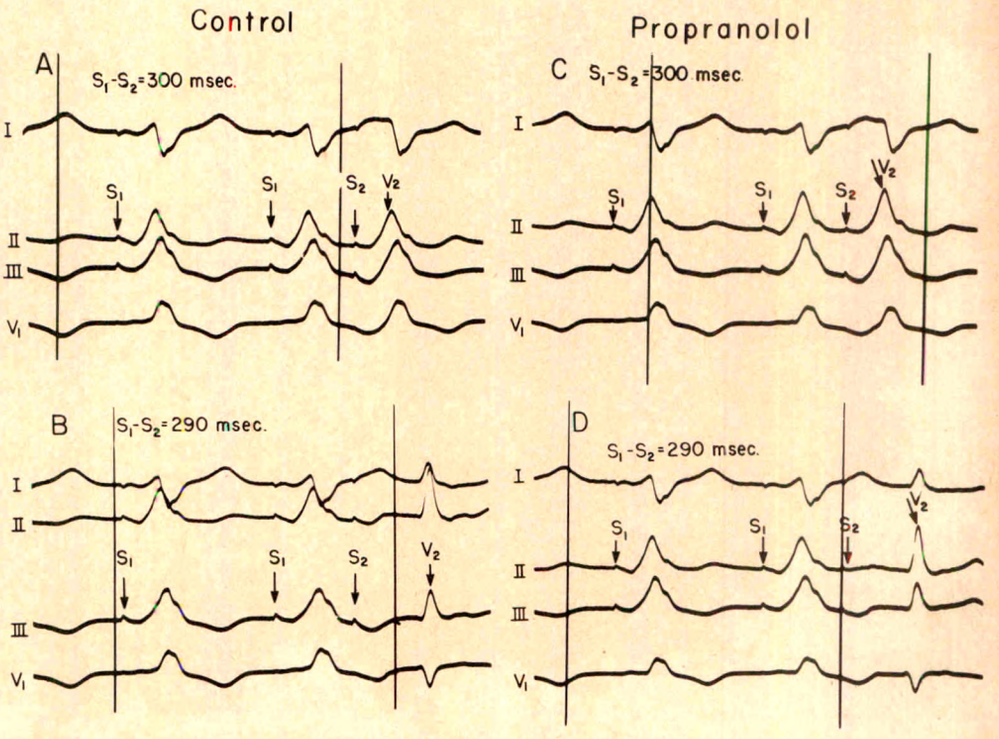


FIGURE 2. Case 6. Determination of anomalous pathway effective refractory period before and after propranolol. For each panel, electrocardiographic leads I, II, III and V_1 are shown. S_1 represents the basic stimulus at a cycle length of 545 msec from the coronary sinus, S_2 the premature atrial stimulus and V_2 the ventricular response to S_2. In this and subsequent illustrations the paper speed is 100 mm/sec and time lines are at 1/sec. **A,** the premature atrial stimulus (S_2) is followed by conduction through the Kent bundle. **B,** the premature stimulus (S_2) is followed by conduction through the atrioventricular node and is blocked in the anomalous pathway (effective refractory period of the anomalous pathway). **C** and **D,** similar to panels **A** and **B,** respectively, after propranolol administration. Note that the effective refractory period of the anomalous pathway remains unchanged after propranolol.

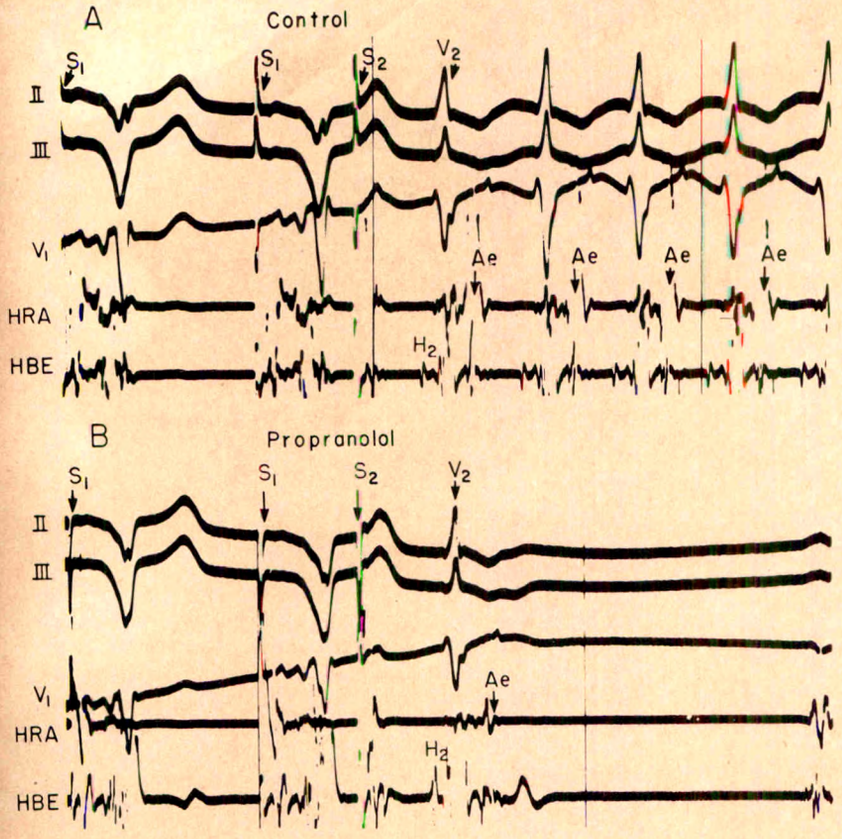


FIGURE 3. Case 3. Failure to induce paroxysmal supraventricular tachycardia after propranolol. In each panel electrocardiographic leads II, III and V_1, the right atrial electrogram (HRA) and His bundle electrogram (HBE) are shown. Right atrial pacing at a cycle length of 600 msec (S_1-S_2 interval) is shown. S_2 is introduced at an S_1-S_2 coupling interval of 310 msec. **A,** before propranolol. After S_2 the impulse is blocked in the anomalous pathway and conducts in anterograde fashion through the normal pathway with induction of sustained atrioventricular (A-V) reentrant supraventricular tachycardia. **B,** after propranolol. As in **A,** the impulse after S_2 (at an identical S_1-S_2 coupling interval) is blocked in the anomalous pathway and conducts through the normal pathway with induction of a single A-V reentrant atrial echo (A_e). The atrial echo is blocked in anterograde fashion in the A-V node, precluding induction of supraventricular tachycardia. A_e = the A-V reentrant atrial echo; H_2 = H is bundle deflection in response to the premature impulse (S_2); other abbreviations as in Figure 2.

measurement of anomalous pathway anterograde refractory period. In two patients, atrial refractoriness limited the measurement of anomalous pathway anterograde refractory period.) Anomalous pathway refractory periods ranged from 280 to 350 msec (304 ± 7.5 msec) during the control period and from 280 to 350 msec (304 ± 8.3 msec) after propranolol (difference not significant). An example is presented in Figure 2.

Twelve patients had intact retrograde anomalous pathway conduction at the maximal tested paced rates of 170 to 220/min (mean ± standard deviation, 196 ± 11/min) both before and after propranolol administration (Table I). In one patient with a left anomalous pathway, retrograde type II A-V block was noted at a paced rate of 180/min before and after propranolol. In five patients, the presence of retrograde anomalous pathway conduction was evident up to maximal paced rates of 170/min both before and after propranolol administration, but was not tested at faster ventricular paced rates.

Anomalous pathway retrograde effective refractory period could be measured in five patients before and after propranolol. Anomalous pathway retrograde refractory periods ranged from 240 to 380 msec (292 ± 27 msec) during the control period and from 250 to 350 (290 ± 19 msec) after propranolol (difference not significant). In 12 patients, ventricular refractoriness limited determination of the anomalous pathway retrograde refractory periods. In these 12 patients the ventricular refractory periods ranged from 340 to 220 msec (258 ± 11 msec) during the control period and 310 to 200 (248 ± 12 msec) after propranolol (difference not significant).

Effects on induction of paroxysmal supraventricular tachycardia: Sustained tachycardia could be induced in 14 patients before propranolol administration with use of the following techniques: (1) atrial extrastimulus technique (8 patients); (2) sudden cessation of rapid atrial pacing (12 patients); (3) cessation of rapid ventricular pacing (8 patients), and (4) ventricular extrastimulus technique (2 patients). In all patients, induced paroxysmal supraventricular tachycardia was characterized by anterograde normal pathway conduction and retrograde anomalous pathway conduction.

In 4 of these 14 patients (29 percent), the ability to induce paroxysmal supraventricular tachycardia was lost after propranolol administration (Fig. 3). In all of these cases, this loss represented an increase in A-V nodal refractoriness that prevented multiple sequential anterograde normal pathway conduction (Fig. 3).

In 10 of these patients (71 percent), induction of sustained tachycardia was possible both before and after propranolol administration using identical stimulatory techniques (Fig. 4). Pre- and postpropranolol tachycardia cycle lengths are presented in Figure 5. Control tachycardia cycle lengths ranged from 270 to 440 msec (mean 328 ± 18 msec). Paroxysmal supraventricular

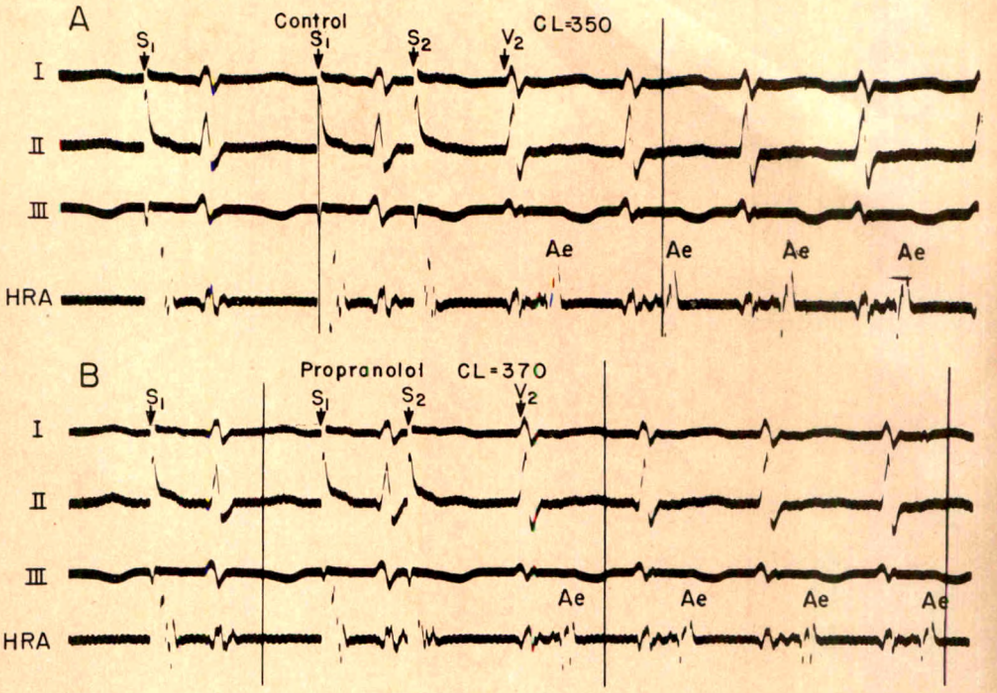


FIGURE 4. Patient 18 (with concealed Kent bundle). Supraventricular tachycardia can be induced before and after propranolol administration. Right atrial pacing at a cycle length (CL) of 500 msec (S_1-S_2 interval) is shown. S_2 is introduced at an S_1-S_2 coupling interval of 280 msec. **A,** induction of paroxysmal supraventricular tachycardia before propranolol. The cycle length of tachycardia is 350 msec. **B,** induction of paroxysmal supraventricular tachycardia after propranolol. The cycle length of tachycardia is 370 msec. Note the small increase in the cycle length of tachycardia. Abbreviations as in Figure 3.

tachycardia cycle lengths after propranolol administration ranged from 300 to 490 msec (mean 352 ± 19 msec) (P <0.01). This change in tachycardia cycle length was equivalent to a decrease in the rate of paroxysmal supraventricular tachycardia of 13 beats/min (heart rate 183 beats/min during control and 170 beats/min after propranolol). The longer cycle lengths after propranolol administration reflected an increase in A-V nodal conduction (A-H interval) during paroxysmal supraventricular tachycardia; the A-H interval measured 162 ± 16.7 msec during the control period and 185 ± 17.1 msec after propranolol (P <0.01).

The H-A interval (measured in the His bundle recordings from the His potential to low right septal atrial electrogram) remained unchanged during tachycardia both before and after propranolol administration. The H-A interval encompassed the H-V interval, QRS duration, anomalous pathway conduction time and intraatrial conduction time.

Echo zones: Reproducible echo zones were delineated with the atrial extrastimulus technique in nine patients both before and after propranolol administration (five patients with manifest preexcitation, one patient with intermittent preexcitation and three patients with concealed preexcitation). During this part of the study, the patient with intermittent preexcitation did not manifest preexcitation and is therefore included in the analysis of echo zones of patients with concealed preexcitation. In the five patients with manifest preexcitation, the outer limit of the echo zone was determined by the anomalous pathway effective refractory period, which was not affected by propranolol administration. In four of the five patients with manifest preexcitation, the inner limit of the echo zone was atrial-limited and shifted to the right, reflecting an increase in atrial effective refractory period after propranolol (258 ± 17 msec versus 277 ± 7 msec; difference not significant). In one patient with manifest preexcitation, the inner limit of the echo zone was shifted to the right and reflected an increased A-V nodal effective refractory period after propranolol. The mean absolute duration of echo zone in the five patients with manifest preexcitation was 40 ± 3 msec during control and 23 ± 5 msec after propranolol administration (difference not significant).

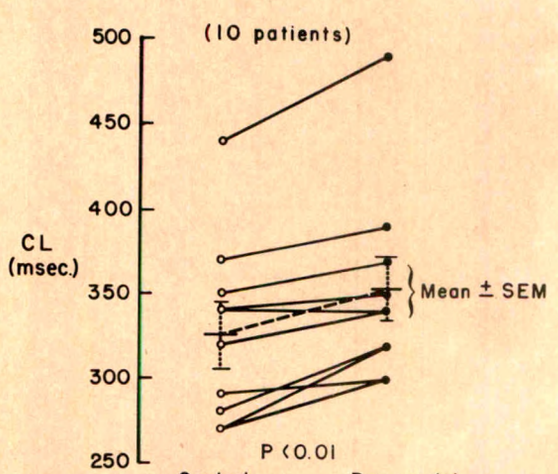


FIGURE 5. Effect of propranolol on the cycle length of induced paroxysmal supraventricular tachycardia before and after propranolol administration. CL = cycle length; P = probability; SEM = standard error of the mean.

In the three patients with concealed preexcitation and in the one with intermittent preexcitation, the outer limit of the echo zone reflected the critical A-V conduction delay necessary for recovery of the anomalous pathway for retrograde conduction.[9] The inner limit of the echo zone in these four patients was limited by atrial refractoriness. The absolute duration of echo zone in these four patients was 67.5 ± 16 msec during the control period and 62.5 ± 28 msec after propranolol administration (difference not significant). In all of these patients, the echo zone was shifted to the right, reflecting greater A-V nodal delay at equivalent coupling intervals after propranolol.

Discussion

Electrophysiologic and pathologic studies suggest that most cases of Wolff-Parkinson-White syndrome reflect the presence of anomalous atrioventricular (A-V) pathways between atria and ventricle.[20] Paroxysmal supraventricular tachycardia complicating the preexcitation syndrome usually reflects circus movements, with the normal pathway as the anterograde limb and the anomalous pathway as the retrograde limb.[20]

The ability to induce paroxysmal supraventricular tachycardia in a patient with two pathways (anomalous pathway and normal pathway) depends on unidirectional block of a premature impulse in one pathway and slow conduction in the other so that the previously blocked pathway is available for conduction of an echo. For example, in patients with manifest preexcitation, the outer limit of the echo zone as determined with the atrial extrastimulus technique usually coincides with the anomalous pathway effective refractory period (in patients whose A-V nodal conduction persists after the anomalous pathway effective refractory period has been reached).[21–24]

Effects of antiarrhythmic agents on the echo zone: Previous studies evaluating the effect of procainamide showed that this drug can effectively prevent induction of paroxysmal supraventricular tachycardia in the majority of patients with preexcitation. This effect is related to the drug's depressant action on retrograde anomalous pathway conduction.[22,25] Sellers et al.[23] observed that procainamide could either increase, decrease or have no effect on the echo interval. Digitalis was reported to abbreviate the echo zone by decreasing anomalous pathway refractoriness and increasing A-V nodal refractoriness.[24]

In this study we did not emphasize quantitation of echo zones for the following reasons: (1) The width of the echo zone depends on the site of stimulation and the distance of this site from both normal and anomalous pathways.[21] Thus, the echo zone is partly an artifact of the location of the pacing electrodes. (2) Most cardiac refractory periods are affected by cycle length (shortening of cycle length decreasing anomalous pathway refractoriness while increasing A-V nodal refractoriness). Therefore, if a given drug abbreviated an echo zone at one cycle length, it is very likely that another effect could be seen at other cycle lengths.[15,21,26] (3) The atrial extrastimulus technique is one of the many means of inducing paroxysmal supraventricular tachycardia in patients with preexcitation. Paroxysmal supraventricular tachycardia can also be induced in such patients with rapid atrial pacing, the ventricular extrastimulus technique and rapid ventricular pacing.[20,27] Therefore, a drug's ability to eliminate an echo zone with the atrial extrastimulus technique does not mean that the drug will totally interfere with induction of tachycardia.

Effects of propranolol on induction of supraventricular tachycardia: For these reasons, we emphasized in this study the presence or absence of the ability (by any technique) to induce paroxysmal supraventricular tachycardia before and after propranolol administration. To summarize our results, propranolol prevented induction of tachycardia in only 4 of 14 patients who manifested inducible supraventricular tachycardia before drug administration. In these four patients, the lack of ability to induce supraventricular tachycardia after propranolol reflected an increase in anterograde A-V nodal refractoriness. In the remaining 10 patients who had induction of tachycardia before propranolol, such induction was possible after drug administration. In these 10 patients, the cycle length of tachycardia increased. In all of the patients in whom anterograde or retrograde anomalous pathway conduction, or both, could be assessed, propranolol had no apparent effect on the ability for anomalous pathway conduction (anterograde or retrograde).

Our results can be interpreted in the following fashion: Because propranolol has no effect on anomalous pathway conduction, it cannot be expected to inhibit sustained tachycardia by depressing such conduction. In regard to the A-V node, propranolol is known to increase A-V nodal refractoriness.[28] In a minority of patients, this increase in A-V nodal refractoriness was sufficient to prevent induction of sustained paroxysmal supraventricular tachycardia by preventing anterograde A-V nodal conduction of rapid sequential impulses. In the majority of patients, the increase in A-V nodal refractoriness was not enough to prevent induction of sustained tachycardia. However, an increase in A-V nodal conduction delay due to propranolol, as manifested by an increase in the A-H interval during paroxysmal supraventricular tachycardia, did increase the cycle length of induced tachycardia.

Clinical implications: Recent electrophysiologic studies in patients with either A-V nodal reentrant supraventricular tachycardia or A-V reentrant supraventricular tachycardia utilizing anomalous pathways suggest that response to acute intravenous drug administration predicts subsequent response to oral administration of the same drug.[29–32] Our present results thus suggest that propranolol alone would prevent attacks of paroxysmal supraventricular tachycardia in only a minority of patients with A-V reentrant paroxysmal supraventricular tachycardia due to manifest or concealed anomalous pathways. In patients in whom propranolol does not prevent attacks of paroxysmal supraventricular tachycardia, one can expect an increase in the cycle length of paroxysmal supraventricular tachycardia. However, the hemodynamic benefits

of this lengthening might well be offset by the negative inotropic effects of propranolol.

In patients with atrial fibrillation and preexcitation, ventricular rate is related to anomalous pathway anterograde refractoriness.[26] Drugs that increase anomalous pathway refractoriness usually slow ventricular rate during atrial fibrillation in patients with preexcitation.[2,22,23,33,34] Because propranolol did not affect anterograde anomalous pathway refractoriness, this drug would probably not slow ventricular rates during atrial fibrillation in patients with preexcitation. If ventricular rates were not slowed with propranolol, the negative inotropic effect of propranolol might be in fact deleterious. Further studies with induction of atrial fibrillation before and after propranolol administration would be necessary to prove this hypothesis.

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Multiple Intracardiac Recordings in Evaluation of Patterns Occurring During Attempted His Bundle Pacing in Man

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The various patterns resulting from stimulation through the catheter electrodes recording His bundle activity were evaluated in 30 patients using intracardiac electrograms from the right ventricular apex (RVA), posterosuperior wall of the left ventricle (LV), high right atrium (HRA) and left atrium (LA) in the vicinity of the coronary sinus. His bundle pacing was characterized by a QRS complex and stimulus (St)-V, St-RVA and St-LV intervals that equaled the QRS configuration, H-V, H-RVA and H-LV intervals of sinus beats. Right septal pacing produced a pattern of "complete" left bundle branch block (with normal electrical axis) associated with St-V intervals of 0 msec, and St-RVA and St-LV intervals of different duration from that of the H-RVA and H-LV intervals recorded during sinus rhythm. Fusion beats resulting from simultaneous activation of His bundle and right septal muscle were characterized by St-V intervals of 0 msec and St-RVA or St-LV intervals of similar duration to that of the H-RVA or H-LV intervals of sinus beats. Fusion QRS configuration depended on the type of ventricular complex present during sinus rhythm. Analysis of the retrograde atrial activation intervals permitted differentiation among impulse initiation at the low right atrium, His bundle or right septal muscle.

Simultaneous recording of multiple atrial and ventricular electrograms has enhanced understanding of the complex patterns observed during attempted His bundle pacing in man.

The validity of His bundle pacing in verifying the origin of a possible His bundle deflection in man has been a subject of considerable debate and speculation.[1–10] In a recent experimental study Williams et al.[11] showed that, as suggested by Narula,[2] simultaneous recording of multiple intracardiac electrograms allowed a more thorough categorization of the various patterns. In view of the potential electrophysiologic interest of this technique, we attempted to determine whether a similar method using catheter electrodes could enhance understanding of His bundle pacing in man.

Material and Methods

Procedure: The technique used in our laboratory to record multiple intracardiac electrograms during atrial and ventricular stimulation has been reported elsewhere.[10,12–14] After the procedure was explained and informed consent obtained from the patient, catheter electrodes were used to record and (or) to pace from the His bundle area, high right atrium (HRA), coronary sinus (CS) and right ventricular apex (RVA). Filtered (40 to 400 hertz and 400 to 500 hertz) electrograms were recorded simultaneously with three surface leads at a paper speed of 100 mm/sec. Atrial and ventricular pacing were performed at rates slightly faster than the spontaneous sinus rhythm using a programmed stimulator that delivered rectangular pulses of 2 msec duration.

After completion of atrial and ventricular stimulation studies, pacing was performed through the bipolar electrodes from which His bundle activity was

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TABLE I

Clinical and Electrophysiologic Data in 30 Patients

Case no.	Age (yr)	Diagnosis	Sinus Rhythm and His Bundle Pacing (msec)				Right Septal Pacing (msec)	
			QRS	H-V (St-V)	H-RVA (St-RVA)	H-LV (St-LV)	St-RVA	St-LV
A. Group 1. Patients With Narrow QRS Complexes								
1	49	RSVT	85	50	60	110	95	140
2	62	PCSD	90	45	65	95	70	130
3	57	PCSD	85	45	60	85	80	140
4	36	RSVT	80	40	65	*	85	*
5	55	RSVT	85	45	60	105	80	145
6	66	SSS	100	50	65	115	70	140
7	68	PCSD	90	45	60	100	70	130
8	54	SSS	80	50	60	*	65	*
9	71	SSS	105	55	60	100	85	135
10	69	PCSD	90	40	55	100	60	145
11	55	RSVT	85	45	60	*	70	130
12	57	RSVT	100	50	70	115	65	150
13	53	SSS	105	70	80	*	90	*
14	49	RSVT	95	45	70	90	60	140
15	66	PCSD	90	40	50	95	90	130
16	44	RSVT	85	50	55	104	85	125
17	59	PCSD	90	45	70	*	100	*
18	67	SSS	105	50	65	110	75	125
19	61	PSCD	100	50	60	105	75	140
20	57	PSCD	90	44	70	95	65	135
21	63	SSS	105	50	55	100	85	150
Range			80–105	40–55†	50–80	85–115	65–100	120–150
B. Group 2. Patients With "Complete" Right Bundle Branch Block								
22	62	PCSD, RSVT, WPW	155	45	100	*	65	*
23	61	PCSD	145	55	105	95	65	130
24	58	PCSD	155	50	105	105	60–65	135
25	64	PCSD	130	55	100	95	75	140
26	66	PCSD, WPW, RSVT	160	45	85	*	60	*
C. Group 3. Patients With "Complete" Left Bundle Branch Block								
27	62	PCSD	130	60	80	180	95	150
28	58	PCSD	150	55	75	170	75	125
29	65	PCSD	145	55	80	175	60	145
30	61	PCSD	140	65	95	180	70	140

* Not measured.
† Except in Case 13.
PCSD = primary conducting system disease; RSVT = recurrent supraventricular tachycardias; SSS = sick sinus syndrome; WPW = Wolff-Parkinson-White syndrome.

recorded, using the same intensity (5 milliamperes), stimulus polarity and cycle length used during ventricular pacing. Lack of capture with this intensity was considered a result of poor electrode positioning requiring slight catheter manipulation. For the purposes of validation five consecutive beats were considered sufficient, as suggested by Narula.[2] In some figures only single beats are shown to enhance the quality (magnification) of the photographic process. Other figures depict the different patterns that could be recorded consecutively during attempted His bundle pacing in man.

Patients: His bundle pacing was attempted in 26 consecutive patients who, during sinus rhythm, had narrow QRS complexes, hereby defined as ventricular complexes of less than 120 msec (Group 1). In addition, information from five (nonconsecutive) patients with "complete" right bundle branch block (Group 2) and from four patients with "complete" left bundle branch block (Group 3) was also included (Table I).

Intervals: The following intervals were analyzed (figures in parentheses indicate normal values in our laboratory):

A-H interval, measured from the onset of the A wave to the beginning of the His deflection in the His bundle electrogram (55 to 120 msec).

H-V interval, measured from onset of the His deflection to the beginning of the QRS complex in the surface electrocardiographic leads (33 to 55 msec). The surface recordings were used to achieve consistency in measurement because the His bundle electrogram was not available for analysis when His bundle pacing was attempted.

A-V interval, measured from the onset of the A wave in the His bundle electrogram to the beginning of the QRS complex in the surface leads. This interval was the sum of the A-H and H-V intervals (90 to 175 msec).

H-right ventricular apex (H-RVA) interval, measured from the onset of the His deflection to the beginning of the right ventricular apex electrogram (40 to 85 msec).[12–16] In the absence of right bundle branch block, this interval represented conduction time through the His bundle, right bundle branch and ordinary ventricular muscle from the site of exit of the right bundle branch to the recording electrodes.

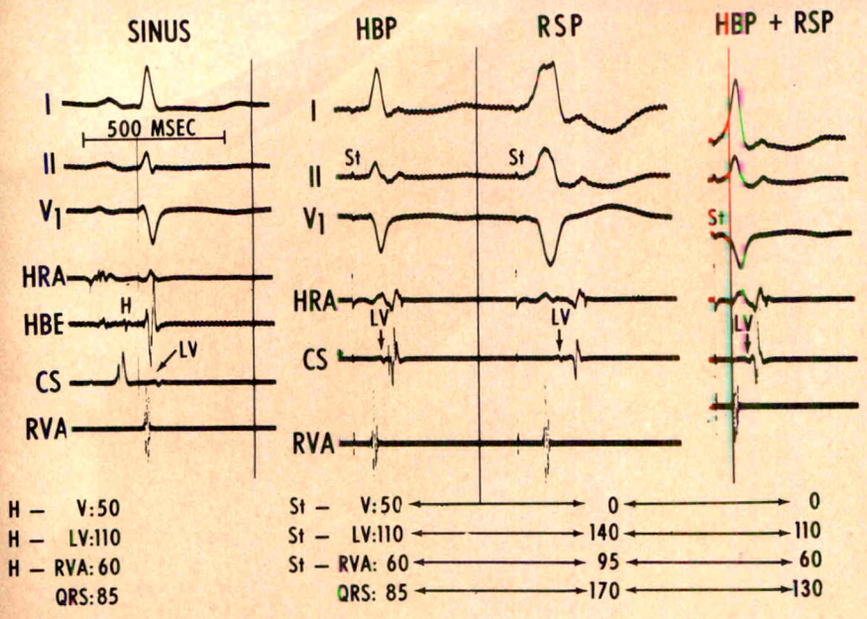


FIGURE 1. Case 1. QRS patterns resulting from His bundle pacing (HBP), right septal ordinary muscle pacing (RSP) and combined His bundle and right septal pacing (HBP + RSP) in a patient with narrow QRS complexes during sinus rhythm (Group 1). During His bundle pacing the atria were activated by the impulse that traversed the atrioventricular (A-V) node in a retrograde direction. Note the slight distortion produced by the retrograde P wave, at the end of the QRS complex. The corresponding St-HRA interval included retrograde A-V nodal and intraatrial conduction time. During right septal pacing the atria were activated by the impulse that penetrated in a retrograde direction the most distal portions of the His-Purkinje system. Thus, the corresponding St-HRA interval is longer than during His bundle pacing. CS = coronary sinus; HBE = His (H) bundle electrogram; HRA = high right atrium; LV = left ventricular electrogram recorded by the catheter in the coronary sinus; RVA = right ventricular apex; St = pacemaker stimulus artifact; V = onset of QRS complex in surface leads.

H-posterosuperior wall of the left ventricle (H-LV) interval, measured from the onset of the His deflection to the beginning of the ventricular electrogram recorded by the catheter in the coronary sinus (85 to 115 msec).[12–16]

Results

Untoward effects did not occur. No patient manifested A-V block, H-V prolongation or splitting of the His bundle potential.

Group 1: Patients With Narrow QRS Complexes

This group comprised only 21 of the consecutive 26 patients, because the number of beats required for validation of the H deflection was not achieved in five patients. The H-V intervals were normal in all but one patient (Case 13) (Table IA). The H-RVA and H-LV intervals were also within normal limits.

His bundle pacing: His bundle pacing without concomitant right septal (inflow tract) ordinary muscle pacing was considered to occur when the stimulus (St)-V, St-RVA and St-LV intervals, as well as the QRS complex, had the same duration (within ± 5 msec) as that of the H-V, H-RVA and H-LV intervals and ventricular complexes of sinus beats. The QRS configuration was also the same (Fig. 1 and 2). In some beats the corresponding P waves produced a distortion of the beginning or end of the QRS complexes (Fig. 1, middle panel).

In three patients manipulation of the catheter, performed to obtain stable His bundle pacing, produced QRS complexes similar in contour to those of sinus origin. The St-V and St-RVA intervals were *longer* than the H-V and H-RVA intervals of sinus (or paced atrial) beats but shorter than the A-V in-

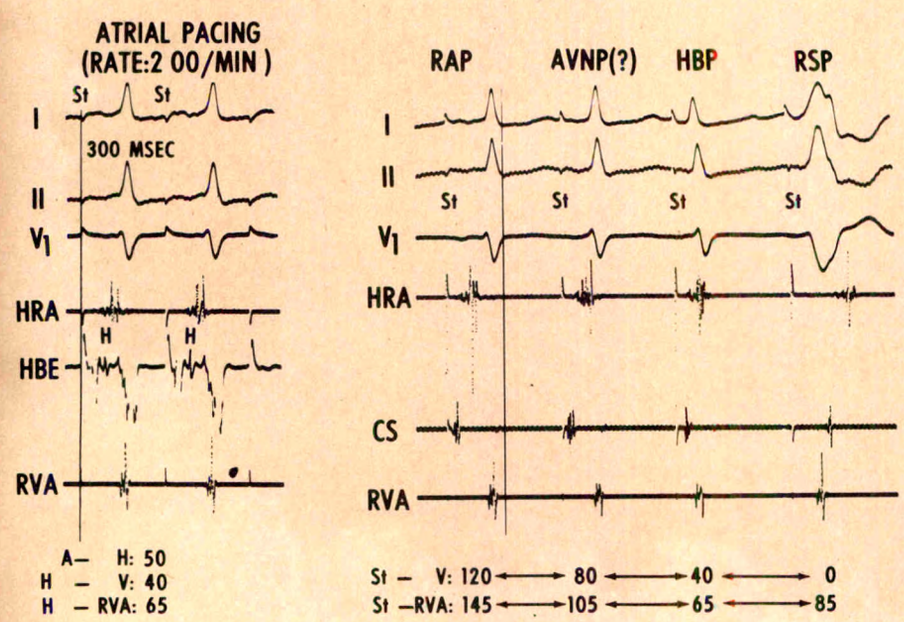


FIGURE 2. Case 4. QRS patterns produced by exclusive low right atrial pacing (RAP), His bundle pacing (HBP), right septal pacing (RSP) and, presumably, atrioventricular nodal pacing (AVNP?) in a patient with narrow QRS complexes (Group 1). St-St intervals in the **left panel** = 300 msec. During His bundle pacing the low right atrium was activated simultaneously with the His bundle. Thus, the St-HRA (high right atrium) interval had the same duration as that occurring during selective low right atrial pacing. Abbreviations as in Figure 1.

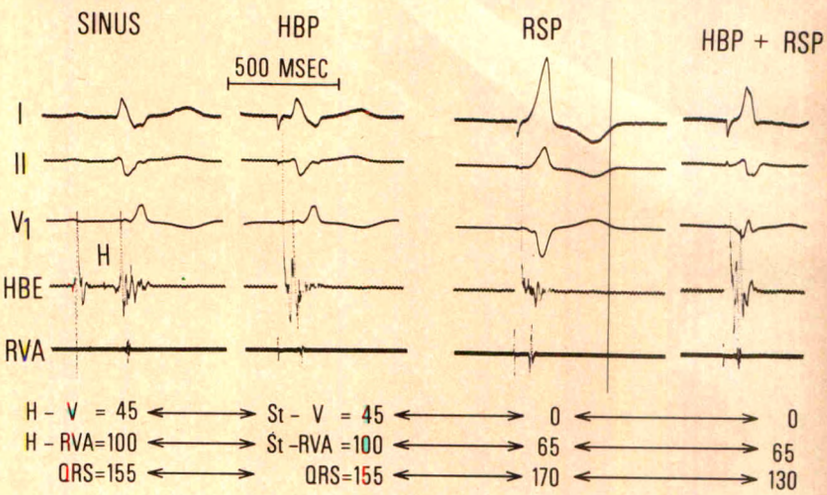


FIGURE 3. Case 22. QRS patterns resulting from His bundle pacing (HBP), right septal pacing (RSP) and combined His bundle and right septal pacing in a patient with "complete" right bundle branch block during sinus rhythm (Group 2). The low right atrium was activated simultaneously with the His bundle during His bundle pacing **(second panel)** as well as during right septal pacing **(third panel)** and combined His bundle pacing and right septal pacing **(right panel).** Abbreviations as in Figure 1.

tervals (second beat of right panel in Fig. 2). These beats probably resulted from stimulation of the atrioventricular (A-V) node itself,[1,2,5] the atrial approaches to the A-V node or partial A-V nodal bypass tracts.

Right septal pacing: Pacing the ordinary ventricular muscle at the right ventricular inflow tract without concomitant His bundle pacing (hereafter called right septal pacing) was characterized by wide (150 msec or more) QRS complexes showing a "complete" left bundle branch block configuration with normal electrical axis (Fig. 1, second beat in middle panel; and Fig. 2, last beat in right panel). The St-V interval measured 0 msec, but the St-LV intervals were longer (120 to 150 msec) than the H-LV intervals of sinus beats (because they now represented conduction time from the paced site to the recording electrodes through the ordinary ventricular muscle).

In these beats the St-RVA intervals represented conduction time from the paced site to the right ventricular apex through the slowly conducting ordinary ventricular muscle.[12–15] Although in individual patients the St-RVA intervals were different (Table IA) from the H-RVA intervals, there was an overlapping when the ranges were compared (St-RVA intervals 65 to 100 msec; H-RVA intervals 50 to 80 msec).

His bundle pacing combined with right septal pacing: Such pacing produced fusion complexes with different configurations that depended on the amount of muscle activated by the wave fronts initiated at the ordinary muscle and His bundle, respectively (Fig. 1, right panel). These fusion beats showed an "incomplete" left bundle branch block configuration with St-V intervals measuring 0 msec. The St-LV and St-RVA intervals had the same duration (±5 msec) as the H-LV or H-RVA intervals of sinus beats (Fig. 1).

In some fusion complexes the right ventricular apex was activated through the ordinary muscle and the left ventricle from the His bundle. In others, the St-RVA and St-LV intervals were similar to those resulting from exclusive right septal pacing, but the QRS complexes were slightly narrower and less distorted. This multiplicity of patterns precluded a thorough analysis of these beats, but we believed that, although the recording right ventricular apical and left ventricular sites had been activated by way of the ordinary muscle, other ventricular areas could still have been depolarized by the wave front emerging from the left branch. However, we could not exclude the possibility that these beats resulted from exclusive right septal pacing from different sites produced by variations of impulse initiation (within the right septal surface due to inadvertent catheter movement).

Group 2: Patients With "Complete" Right Bundle Branch Block

The H-V interval did not exceed the upper limits of normal in any of the five patients in this group (Table IB). However, the H-RVA interval was prolonged (range 85 to 105 msec) because the right ventricular apex was now activated by the wave front initiated at the left septal surface (Fig. 3). The H-RVA interval thus resulted from the sum of the H (left septal)-V and (left septal) V-RVA intervals.[12–16] The H-LV interval was of normal duration (95 to 105 msec) in the three patients in whom it was measured.

His bundle pacing: This was characterized, as in patients with normal intraventricular conduction, by St-LV and H-RVA intervals and QRS complexes of similar duration to the H-LV and H-RVA intervals and ventricular complexes of sinus beats (Fig. 3).[10]

Right septal pacing: As in patients with normal intraventricular conduction (Group 1), right septal pacing was also characterized by wide QRS complexes with a "complete" left bundle branch block–normal axis pattern, St-V interval of 0 msec and St-LV interval of longer duration than the H-LV interval (130 to 140 msec).[10] However, the St-RVA interval (60 to 75 msec) was shorter than the H-RVA interval (85 to 105 msec), because the conduction time from paced (right septal) site to right ventricular apex was shorter than the conduction time from His bundle to left septal surface, and from the latter to the right ventricular apex.

Combined His bundle and right septal pacing: This produced an "incomplete" right bundle branch block pattern with absent S waves in lead I and qR complexes in V_1 (Fig. 3, right panel).

Group 3: Patients With "Complete" Left Bundle Branch Block

Because none of the four patients in this group had abnormal (beyond −30°) left axis deviation, the following description applies only to patients having "complete" left bundle branch block with a normal electrical axis (Table IC).

His bundle pacing: During His bundle pacing the St-LV and St-RVA intervals, as well as QRS configuration, were similar to the H-LV and H-RVA intervals and QRS contour

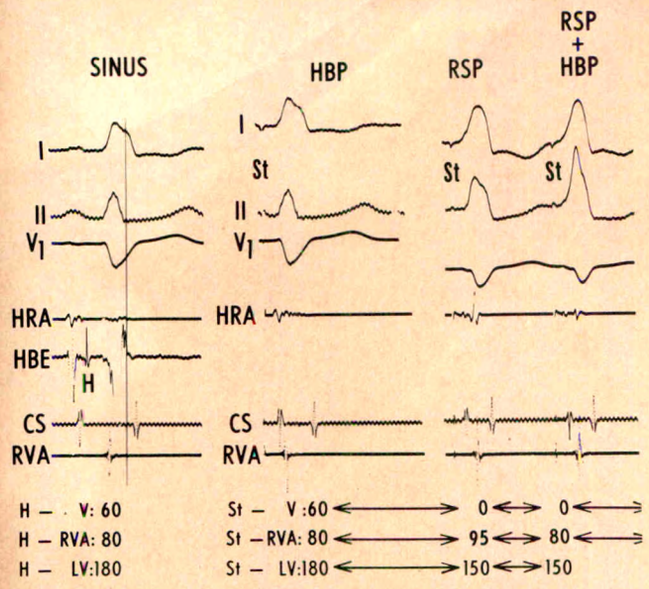


FIGURE 4. Case 27. QRS patterns resulting from His bundle pacing (HBP), right septal pacing (RSP), and, presumably, combined right septal and His bundle pacing in a patient with "complete" left bundle branch block during sinus rhythm (Group 3). The low right atrium was activated simultaneously with the His bundle during His bundle pacing **(middle panel)** as well as in combined pacing **(right panel).** Abbreviations as in Figure 1.

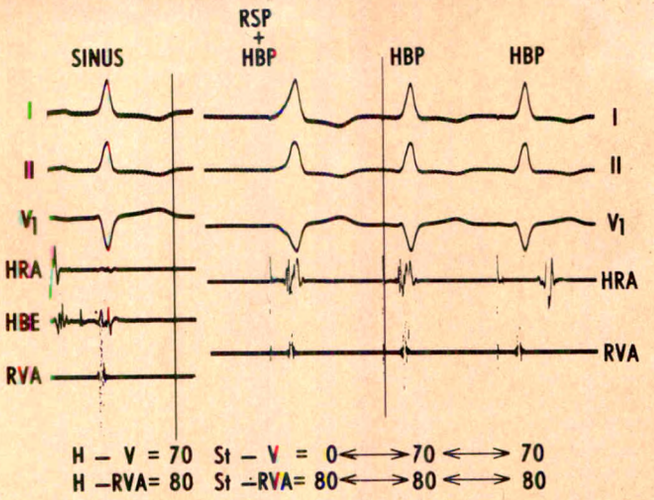


FIGURE 5. Case 13. QRS complexes resulting from His bundle pacing (HBP) and combined His bundle pacing and right septal pacing (RSP + HBP) (Group 1). Whereas the low right atrium was activated simultaneously with the His bundle in the first two beats of the right panel, it was activated by the impulse traversing the node in a retrograde direction in the last beat. This St-HRA (high right atrial) interval, therefore, was longer than the preceding St-HRA interval. Abbreviations as in Figure 1.

of sinus beats (Fig. 4, middle panel). However, the St-LV and H-LV intervals were longer than in Groups 1 and 2 because these intervals now represented the conduction time from the His bundle to the right septal surface (H-V intervals), and from the latter to the recording electrodes in the posterosuperior wall of the left ventricle (Fig. 4, middle panel).[12–15]

Right septal pacing (without concomitant His bundle pacing): This procedure produced QRS complexes with a "complete" left bundle branch block-normal axis pattern but of a different configuration from that of sinus beats. The St-LV interval was shorter (125 to 150 msec) than the H-LV interval of sinus beats (170 to 180 msec). The St-RVA interval was different (shorter in two and longer in one) than the corresponding H-RVA interval. In one case the St-RVA and H-RVA intervals had a similar duration.

Combined His bundle and right septal pacing: The differentiation between right septal pacing (without concomitant His bundle pacing) and fusion beats resulting from combined right septal pacing and His bundle pacing could not be made with certainty (Fig. 4) because fusion beats did not produce narrow QRS complexes with a pattern of "incomplete" left bundle branch block. It could be assumed, but not proved, that QRS complexes of less width than those attributed to right septal pacing could be fusion beats if the St-RVA or St-LV interval had the same value as the H-RVA or H-LV interval of sinus beats (right panel of Fig. 4).

Atrial Activation Sequences

His bundle pacing occurred simultaneously with low right atrial pacing in 21 patients (Fig. 2, right panel; Fig. 3, second panel; Fig. 4, second panel and Figure 5, right panel). This was characterized by St-HRA and St-LA intervals of shorter duration than those occurring when (in 13 patients) selective His bundle pacing resulted in retrograde conduction through the A-V node (Fig. 1, second panel, and Fig. 5, right panel).

Fusion beats, produced by combined His bundle and right septal pacing, coexisted with simultaneous low right atrial stimulation in 26 patients (Fig. 1, 3 and 5).

Right septal pacing was associated with retrograde conduction to the atria (14 patients) or with simultaneous pacing of the low right atrium (8 patients). During the former, the St-HRA and St-LV intervals were even longer than when the His bundle was simultaneously paced (Fig. 1, middle panel, and Fig. 2, right panel). However, during the latter the intervals were similar to those occurring with low right atrial pacing (Fig. 3, third panel, and Fig. 4, right panel).

Discussion

Multiple intracardiac electrograms in evaluation of the St-V interval and QRS configuration observed during attempted His bundle pacing: Some investigators[1–5] have stated that His bundle pacing is the simplest, the most direct and even the only definite method of validation of a bundle of His (H) deflection and have published clinical examples to support these assumptions. However, other authors[6–8] have questioned these statements on several grounds including the production of multiple patterns such as "supraventricular" beats, "fusion" beats and "bizarre" ventricular beats.

The multiple catheter technique in our cases permitted the categorization of the QRS configuration due to His bundle pacing, right septal pacing and (some) fusion beats resulting from combined His and right septal pacing. Evidently, a purist might claim that the diagnosis of selective His bundle pacing can never be made if he argues that one cannot rule out that the stimulus produced depolarization of a small group of ordinary muscle cells at the right ventricular inflow tract that was not translated into QRS or T wave changes in

the surface leads. In this sense, some beats considered due to exclusive His bundle pacing can be interpreted as "microfusion" beats. A similar argument can be used to deny the existence of the pseudofusion beats that have been described in patients with QRS-inhibited pacemakers.[17]

Latency and His bundle pacing: It has been said that the St-V interval recorded in the surface leads need not be ascribed to His bundle pacing but to ("true") latency between the stimulus and the recorded onset of depolarization, which may be prolonged by the electrode-tissue interface created by the free-floating catheter.[6] The relevance of this criticism is minimized by the repeated demonstration in clinical and experimental studies[1,4,11,18,19] of the good correlation between the intervals recorded during sinus rhythm and His bundle pacing. Moreover, A-V nodal stimulation or A-V nodal bypass tract stimulation (and not necessarily "true" latency) can result in beats of supraventricular contour in which the St-V, St-RVA and St-LV intervals are longer than the H-V, H-RVA and H-LV intervals but shorter than the A-V, A-RVA and A-LV intervals (Fig. 2).[1,2,5]

Validation of an H deflection during combined His bundle pacing and right septal pacing: Williams et al.[11] stated that in the experimental laboratory combined His bundle pacing and right septal pacing constituted validation of an H potential. Yet they considered that in clinical practice misinterpretation could result if only the St-V and QRS criteria were used. Our study corroborates their assumption that, *once His bundle pacing has been achieved,* fusion beats resulting from such pacing combined with right septal pacing can also validate an H potential. In our series the mere presence of fusion beats (without clear-cut His bundle pacing) did not validate the results of His bundle pacing because a similar configuration can result (in some cases) from exclusive right septal pacing.

Differences between catheter techniques of His bundle pacing in human and canine hearts: In the human heart *persistent* His bundle pacing cannot be performed with the same consistency as when plunge electrodes are used in experimental studies. Narula[2] suggested that three to five consecutive paced beats constitute validation because it is difficult to maintain the catheter over the His bundle area for long periods of time in the precise position required for "selective" His bundle pacing (that is, His bundle pacing without right septal stimulation). If this criterion had been extended so as to require a single paced beat, then His bundle pacing would have been achieved in all of our patients.

Experimental studies have shown that a good H deflection can be recorded from a greater distance than that required for selective His bundle pacing, thereby explaining why it is easier to record than to pace the His bundle.[2] Moreover, stimulus polarity and stimulus intensity play an important role in the genesis of the patterns produced by pacing of the A-V region.[2,5,9,11] In our study these variables were kept constant as they usually are during clinical pacing or during conventional studies with the extrastimulus method.

Differences between the catheter technique and direct stimulation: Differences were also noted between our findings and those of Kupersmith et al.,[9] who used probe electrodes and stimuli of varying intensity to perform His bundle pacing in 26 patients during cardiopulmonary bypass. These differences are probably related to the techniques used. For instance, the interelectrode distance of the probe electrode was 1 or 2 mm, whereas that of our catheter electrode was 10 mm. The greater interelectrode distance can produce stimulation of larger areas, hence facilitating simultaneous pacing of the atria and ventricles as well as different ventricular activation sequences (QRS patterns) resulting from stimulation of a greater ventricular muscle mass.

Atrial activation sequences: In our study, analyses of the atrial activation sequences and of the timing of the arrival of the excitation at the recording electrodes in the high right atrium and left atrium in relation to the onset of the pacing stimulus allowed us to determine whether the atria were activated in retrograde manner by impulses initiated in a low right atrial site, the His bundle or the ordinary right septal muscle.

Clinical implications: His bundle recordings are being performed with increasing frequency in cardiovascular laboratories (and in coronary care units) throughout the world. However, His bundle pacing, which is of potential value in validating the origin of a given deflection, has not gained widespread acceptance. An almost insurmountable difficulty, which cannot be resolved by recording only one or two intracardiac leads, is the interpretation of the multiple atrial and ventricular activation patterns that occur when this procedure is attempted. These have been described as "supraventricular," "fusion" and bizarre ventricular beats.[6–8] For this reason, pacing through the catheter electrode recording His bundle activity has been, in our opinion, the least understood form of electrical stimulation in man. In spite of certain limitations, our data can enhance the comprehension of the various QRS patterns and activation sequences occurring during attempted His bundle pacing in the human heart. The value of St-RVA and St-LV interval measurements in patients with "complete" left bundle branch block in differentiating the "normalized" narrower QRS complexes resulting from distal His bundle pacing from the patterns resulting from right bundle branch stimulation is currently being evaluated.

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- Catapres lowers blood pressure promptly.
- No contraindications.
- Some patients may have dry mouth, drowsiness, and sedation. Tell them that these tend to diminish with continued use.
- Giving the larger part of the divided dose at bedtime can help alleviate drowsiness and sedation.

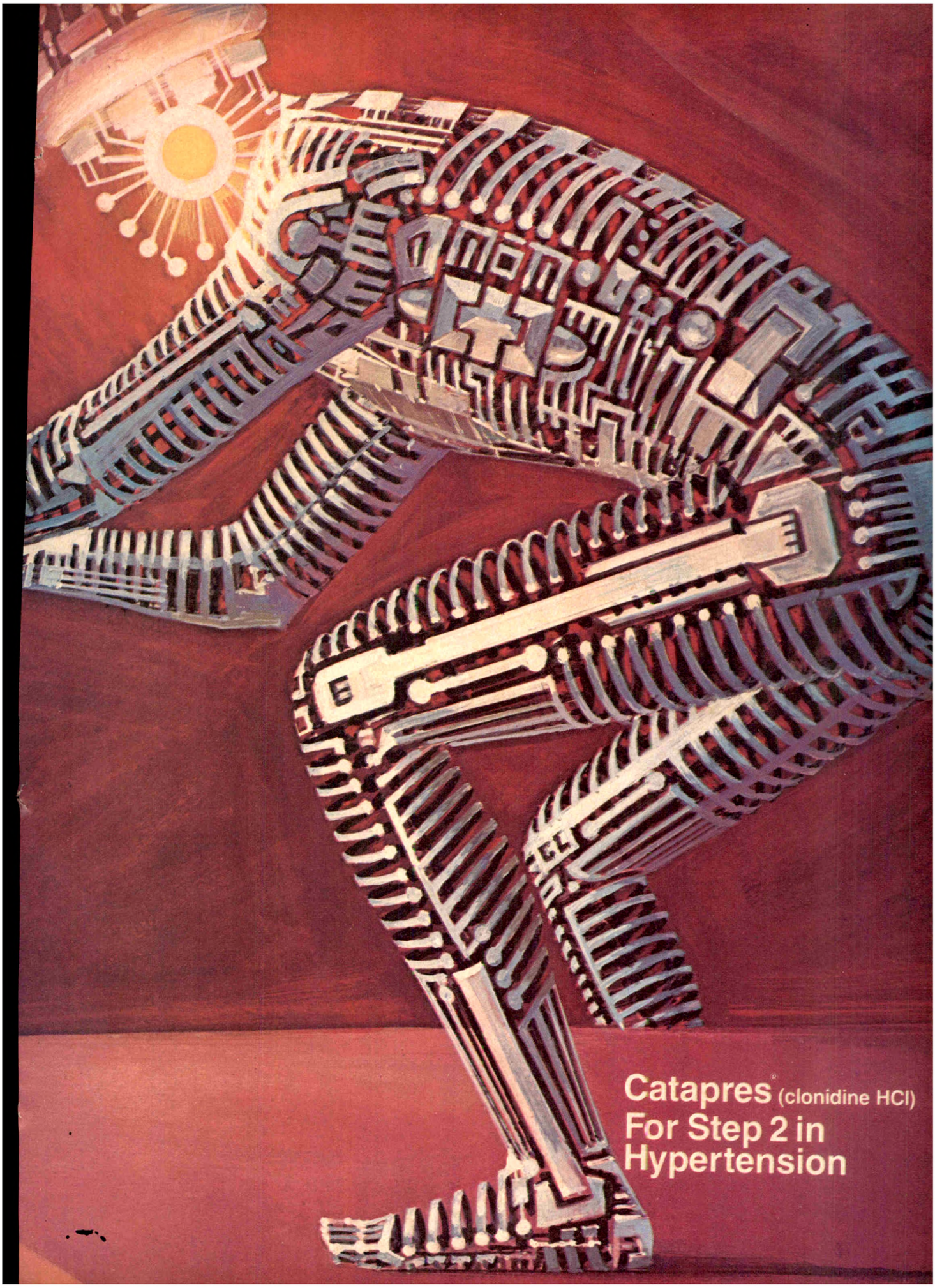
The next 20 years*

- Lowered blood pressure.
- Little impotence, depression or postural hypotension.
- No fatal hepatotoxicity in over a decade of worldwide use.
- Broad therapeutic dosage range to keep step with changing dosage needs over the years.

*Tolerance may develop in some patients, necessitating a reevaluation of therapy.

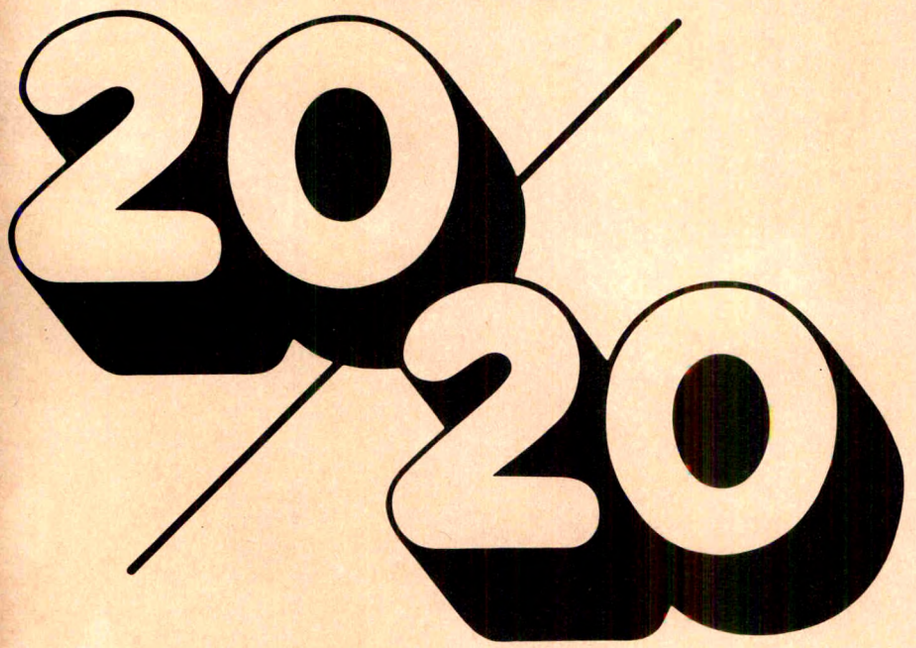
For full details on adverse reactions, warnings, and precautions, see brief summary of the prescribing information on last page of this advertisement.




Catapres® (clonidine HCl)
For Step 2 in
Hypertension

A New Vision of Catapres® (clonidine HCl)

Tablets of 0.1 and 0.2 mg



What you do the first 20 days Can help him the next 20 years

Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in poten It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetu
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consultin their physician. Rare instances of hypertensive enceph lopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pres sure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machiner or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any oth agent lowering blood pressure, clonidine hydrochlorid should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochlorid should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continue therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established. These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver func tion tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patien receiving clonidine hydrochloride, chlorthalidone, and papaverine hydrochloride. Weight gain, transient eleva tion of blood glucose, or serum creatine phosphokinas congestive heart failure, Raynaud's phenomenon; vivi dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and ment depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of th eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somno lence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of ar analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage

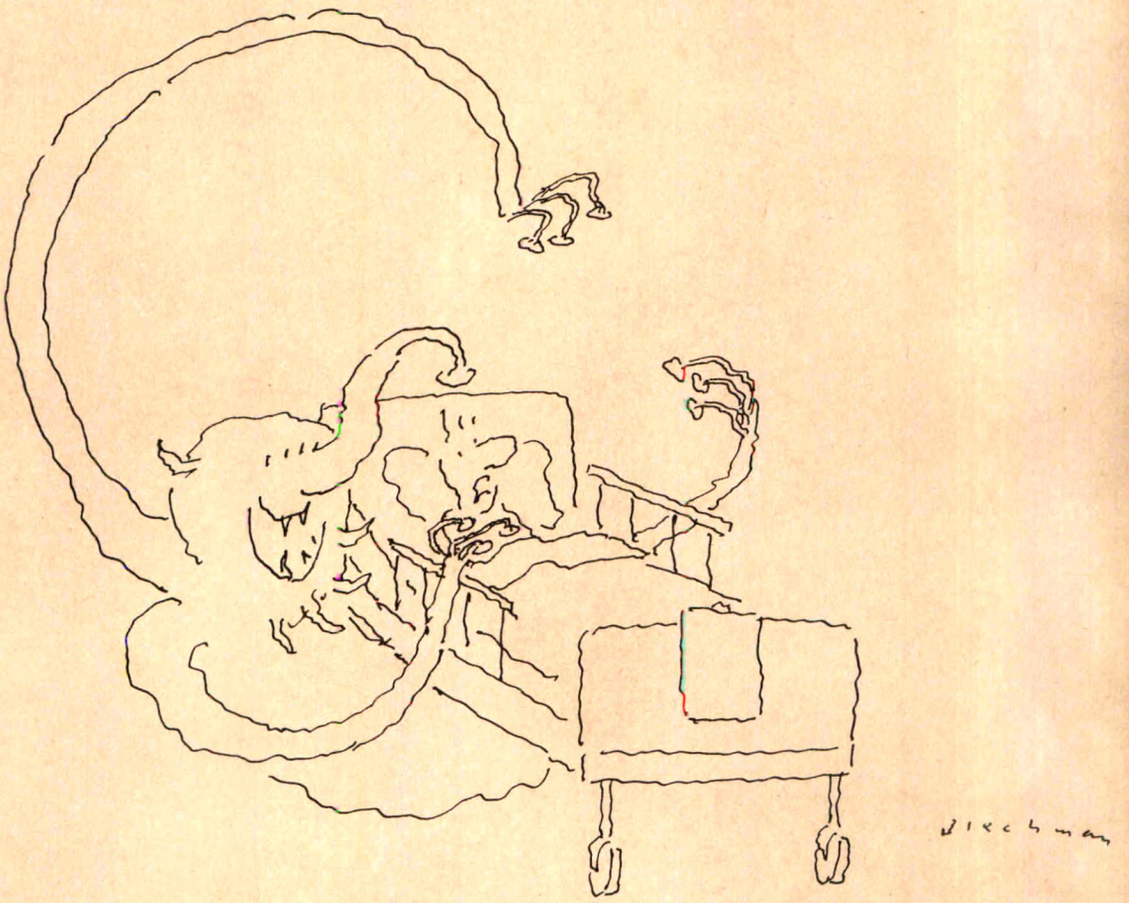
How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000.

For complete details, please see full prescribing information.

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Ridgefield, CT 07687

an itchy electrode can assume strange proportions.



To a person who's critically ill in strange surroundings and feeling scared, even a little thing like an itchy electrode can seem monstrous.

That's why we make Red Dot® Brand Monitoring Electrodes the way we do. With a special emphasis on patient comfort.

Red Dot Electrodes offer the benefits you expect from a product of this kind—reliable, clear tracings and adhesive strength. Plus something special:

A backing of Micropore® Brand Surgical Tape, which permits the skin to ventilate freely. And the adhesive is hypoallergenic, which eliminates a major cause of skin irritation. It'll adhere firmly, even to perspiring patients, and for extended periods of time.

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Please send me a Red Dot Electrode sample kit for evaluation.

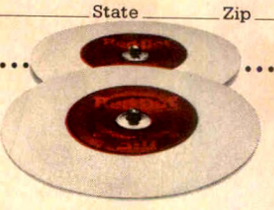
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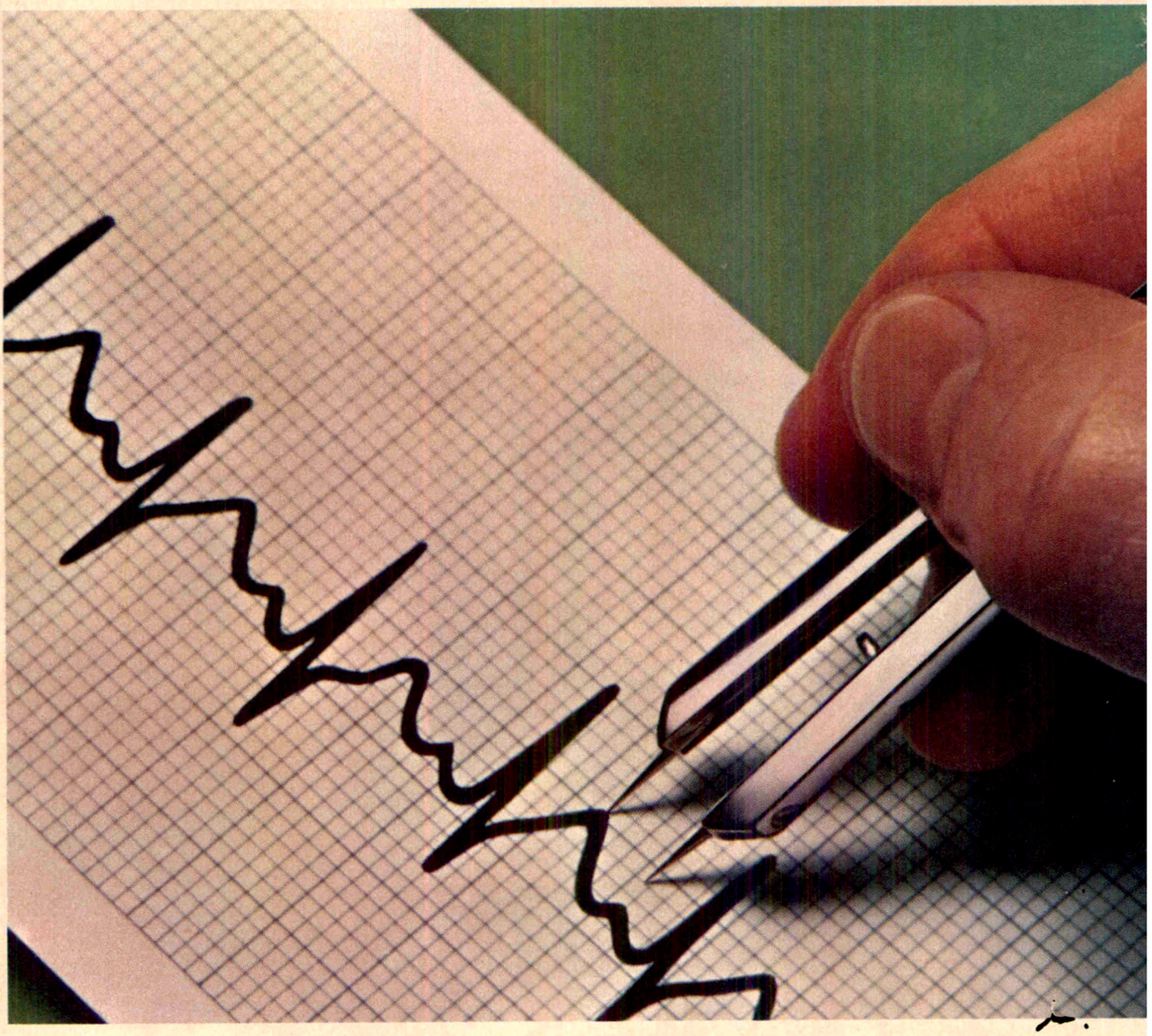


3M COMPANY

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INDERAL®
(propranolol hydrochloride)
PERFORMANCE IN CARDIAC ARRHYTHMIAS

EFFECTIVE ALONE OR IN COMBINATION



INDERAL (propranolol hydrochloride): Successful treatment of supraventricular arrhythmias for over 10 years

INDERAL, used alone or in combination with other antiarrhythmics, has improved or resolved a variety of supraventricular arrhythmias.[1-7]

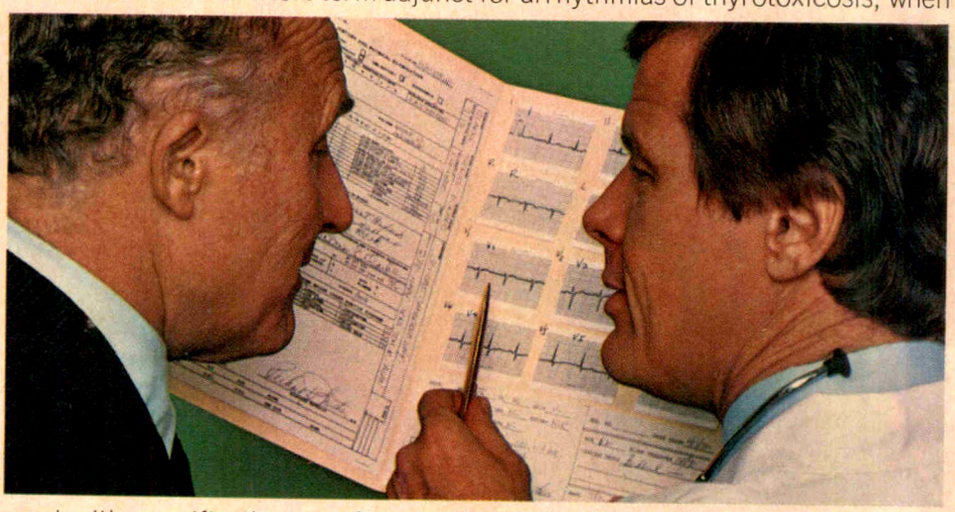
INDERAL alone: Results of use against atrial tachyarrhythmias in one series have recently been reported:

Arrhythmia	Patients	Proportion deriving benefit	
		Complete	Partial
Sinus tachycardia	86	59%	22%
Atrial tachycardia (including paroxysmal type)	154	61%	19%
Atrial flutter	50	54%	32%
Atrial fibrillation	139	53%	26%

Adapted from Coodley and Snyder.[8]

INDERAL is particularly effective in therapy of supraventricular tachyarrhythmias.[9] It slows depolarization of sinus and ectopic pacemaker cells, and retards impulse-conduction in the atria and across the AV node.[1,10,11] In cases where it cannot restore normal sinus rhythm, INDERAL is frequently effective in reducing the ventricular rate.[1-3,12-14] INDERAL may prevent recurrent supraventricular tachyarrhythmias when digitalis and quinidine fail to do so.[9,12] In addition, INDERAL is a useful short-term adjunct for arrhythmias of thyrotoxicosis, when





used with specific therapy. Since INDERAL may mask the clinical signs of hyperthyroidism, abrupt withdrawal should be avoided to prevent exacerbation of the symptoms of hyperthyroidism.

And in combination: INDERAL has also been used to complement the actions of other antiarrhythmic agents.[3-5,8,9,13] The combination of INDERAL and quinidine has suppressed supraventricular arrhythmias that have not responded to either drug alone.[3,9]

When toxic doses of digitalis glycosides occasionally fail to control the ventricular rate in patients with atrial fibrillation or flutter, addition of INDERAL to a digitalis glycoside, with reduction of the digitalis dosage, may prolong AV conduction to the point where satisfactory control of ventricular rhythm is established.[8,15]

INDERAL: Often effective in tachyarrhythmias of digitalis intoxication[2,9,10,14] INDERAL has been found useful in the treatment of certain digitalis-induced arrhythmias that persist following discontinuation of digitalis and correction of electrolyte disturbances, particularly hypokalemia. Its use in this setting may be limited by the presence of significant congestive failure or heart block, and the development of severe bradycardia. (Please see prescribing information on the next page for "Overdosage or Exaggerated Response.")

INDERAL is contraindicated in sinus bradycardia, greater than first degree heart block, and congestive heart failure unless the failure is secondary to tachyarrhythmias treatable with INDERAL. (See prescribing information for complete list of CONTRAINDICATIONS.)

Please see next page for prescribing information.

Ayerst

BRIEF SUMMARY
(For full prescribing information, see package circular.)

INDERAL® Brand of propranolol hydrochloride

A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS: INDERAL is a beta-adrenergic receptor blocking drug, possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available beta receptor sites. When access to beta receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and one-half hours. The biologic half-life is approximately two to three hours. Propranolol is not significantly dialyzable. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade and this appears to be its principal antiarrhythmic mechanism of action. The membrane effect also plays a role, particularly, some authorities believe, in digitalis-induced arrhythmias. Beta-adrenergic blockade is of unique importance in the management of arrhythmias due to increased levels of circulating catecholamines or enhanced sensitivity of the heart to catecholamines (arrhythmias associated with pheochromocytoma, thyrotoxicosis, exercise).

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential and depresses cardiac function.

INDICATIONS: Cardiac Arrhythmias

1.) Supraventricular arrhythmias

a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.)

b) Persistent sinus tachycardia which is noncompensatory and impairs the well-being of the patient.

c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy.

May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS.)

d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures.

e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

2.) Ventricular tachycardias

Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias.

a) Ventricular tachycardias

With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice. In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered. If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly. (See DOSAGE AND ADMINISTRATION.) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.*

b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

3.) Tachyarrhythmias of digitalis intoxication

If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur. (See OVERDOSAGE OR EXAGGERATED RESPONSE.)

Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION.)

4.) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia

Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, INDERAL may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. (See WARNINGS.)

Hypertrophic Subaortic Stenosis: INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of INDERAL in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.

Pheochromocytoma: After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use INDERAL (propranolol hydrochloride) unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS: INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS: CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely. a) If cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the signs of clinical developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function; beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS: Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS: *Cardiovascular:* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura

Central Nervous System: lightheadedness; mental depression manifested by insomnia; lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea; constipation

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION: The dosage range for INDERAL (propranolol hydrochloride) is different for each indication.

ORAL

ARRHYTHMIAS—10-30 mg three or four times daily, before meals and at bedtime.

HYPERTROPHIC SUBAORTIC STENOSIS—20-40 mg three or four times daily, before meals and at bedtime.

PHEOCHROMOCYTOMA—*Preoperatively*—60 mg daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.

—*Management of inoperable tumor*—30 mg daily in divided doses.

PEDIATRIC DOSAGE: At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS: Intravenous administration is reserved for life-threatening arrhythmias or those occurring under anesthesia. The usual dose is from 1 to 3 mg administered under careful monitoring, *e.g.*, electrocardiographic, central venous pressure. The rate of administration should not exceed 1 mg (1 ml) per minute to diminish the possibility of lowering blood pressure and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the site of action even when a slow circulation is present. If necessary, a second dose may be given after two minutes. Thereafter, additional drug should not be given in less than four hours. Additional INDERAL should not be given when the desired alteration in rate and/or rhythm is achieved.

Transference to oral therapy should be made as soon as possible.

The intravenous administration of INDERAL has not been evaluated adequately in the management of hypertensive emergencies.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg). IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY.

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS

HYPOTENSION—VASOPRESSORS, *e.g.*, LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE

HOW SUPPLIED: INDERAL (propranolol hydrochloride)

TABLETS

No. 461—Each scored tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 464—Each scored tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 468—Each scored tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

INJECTABLE

No. 3265—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 ml ampuls in boxes of 10.

REFERENCES: 1. Shand, D.G.: N. Engl. J. Med. *293*:280 (Aug. 7) 1975. 2. Conn, R.D.: Postgrad. Med. *55*(No. 2):131 (Feb.) 1974. 3. Fors, W.J., Vanderank, C.R., and Reynolds, E.W.: Am. J. Cardiol. *27*:190 (Feb.) 1971. 4. Levi, G.F., and Proto, C.: Cardiology *55*:249, 1970. 5. Stern, S.: Am. Heart J. *74*(No. 2):170 (Aug.) 1967. 6. Luria, M.H., Adelson, E.I., and Miller, A.J.: Circulation *34*:767 (Nov.) 1966. 7. Gianelly, R.E., Griffin, J.R., and Harrison, D.C.: Ann. Intern. Med. *66*:667 (Apr.) 1967. 8. Coodley, E.L., and Snyder, S.: Am. Fam. Physician *14*(No. 5):146 (Nov.) 1976. 9. Miller, R.R., Amsterdam, E.A., and Mason, D.T.: Drug Therapy *5*:110 (Feb.) 1975. 10. Danahy, D.T., and Aronow, W.S.: Postgrad. Med. *61*(No. 1):113 (Jan.) 1977. 11. Gettes, L.S.: Med. Opinion *5*(No. 9):19 (Sept.) 1976. 12. Gianelly, R.E., and Harrison, D.C.: Geriatrics *25*:120 (Apr.) 1970. 13. Michaelson, S.P., and Wolfson, S.: Cardiovasc. Med. *1*(No. 3):213 (Nov.) 1976. 14. Wit, A.L., Hoffman, B.F., and Rosen, M.R.: Am. Heart J. *90*(No. 5):665 (Nov.) 1975. 15. Bigger, J.T., and Giardina, E.G.V.: Cardiovasc. Clin. *6*(No. 2):103, 1974.

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Pharmacologic and Behavioral Effects on Arrhythmias That Immediately Follow Abrupt Coronary Occlusion: A Canine Model of Sudden Coronary Death

JON ROSENFELD, MD, PhD
MICHAEL R. ROSEN, MD, FACC
BRIAN F. HOFFMAN, MD

New York, New York

We have developed and studied a chronically instrumented canine model in which occlusion of a major coronary artery by an implanted balloon occluder promptly leads to arrhythmias that are reasonably reproducible on successive occlusions. Dogs were studied while conscious, and the electrocardiogram and electrograms from ischemic and nonischemic ventricular epicardium were recorded. Either the left anterior descending or circumflex coronary artery was occluded for up to 5.5 minutes. Experiments were performed in a carefully controlled environment at intervals sufficient for full recovery between occlusions. The arrhythmias that occurred were single or multiple premature ventricular depolarizations, runs of ventricular premature depolarizations or ventricular fibrillation. We measured the time from the onset of occlusion to the onset of arrhythmia (latency) and the severity of the arrhythmia (grade). Latency increased with successive occlusions in the same environment until no arrhythmia occurred during an occlusion of 5.5 minutes. In this state, addition of behavioral stress usually led to recurrence of arrhythmia. Stress decreased latency ($P < 0.02$) and increased grade. We also studied the effects of tolamolol (a beta blocking agent), UM-272 (an analog of propranolol) and diazepam. Tolamolol increased latency ($P < 0.02$) and tended to decrease grade. UM-272 had variable effects, but it clearly did not exert a protective action. The severity of arrhythmia was inversely related to latency, and latency decreased with increases in heart rate. The results obtained indicate that the model is useful for studies on arrhythmias that follow soon after the onset of ventricular ischemia, and they emphasize the relation between stress, enhanced sympathetic activity and ventricular arrhythmias.

Sudden coronary death is a leading cause of death among adults. The abruptness with which it strikes complicates medical care of its potential victims and precludes adequate study of the events that immediately precede death. The development of suitable animal models of this syndrome is needed to advance understanding of its pathophysiology and the means for its prevention. Both sudden coronary death in man and death after experimental coronary occlusion in dogs follow a time course of a few minutes. In man the initiating cause most often is compromised coronary flow that leads to ventricular fibrillation.[1–4] In the dog, a sudden reduction in coronary flow through a major vessel leads to a similar sequence of ventricular arrythmias.[5,6] These common factors suggest that the arrhythmias that result from abrupt coronary occlusion in the dog might provide a good model of the sudden coronary death syndrome.

Prior studies on other models[7–14] have suggested that these arrhythmias may be influenced by behavioral stress, altered sympathetic neural tone, beta adrenergic blockade, individual variations in coronary anat-

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omy or the site of occlusion, and the effects of anesthesia and thoracotomy. For these reasons one should study conscious animals in which coronary occluders are implanted chronically so that repeated experiments can be performed on a single animal and each animal can act as its own control for intervention trials. Such a model would be suitable for evaluating the effects on arrhythmias of behavioral and environmental factors. This study was undertaken to develop such a model and to use it to evaluate the effects of stress and several pharmacologic agents on the arrhythmias caused by sudden coronary occlusion.

In selecting the pharmacologic agents used we attempted to consider two major possibilities. The first was that an increase in efferent sympathetic activity, as might be caused by pain or apprehension, would increase the likelihood of early lethal arrhythmias. The second was that the direct cardiac depressant effects of traditional antiarrhythmic drugs, and the direct cardiac effect of the beta adrenergic blocking agent propranolol, also might predispose to early lethal arrhythmias. For this reason we selected the experimental beta adrenergic blocking drug tolamolol, which is almost devoid of direct local anesthetic-like effects on the heart[15] and compared it with the quaternary analog of propranolol, UM-272 (N,N-dimethyl-1-isopropylamino-3-[1-naphthyloxy]-propan-2-ol), which causes no beta adrenergic blockade[16] but exerts direct effects on the heart similar to those of the local anesthetic antiarrhythmic agents.[17] Also, to evaluate the possibility that adverse effects of stress might be attenuated by an antianxiety drug, we studied the effects of diazepam. The studies showed that stress does exert an undesirable effect on the arrhythmias that occur soon after coronary occlusion and that both diazepam and tolamolol delay the onset and reduce the severity of such arrhythmias.

Methods

Experimental model: Young adult mongrel dogs of both sexes weighing 12 to 27 kg were selected on the basis of apparent good health and reasonable disposition. They were anesthetized intravenously with sodium pentobarbital, 30 mg/kg body weight. Antibiotic prophylaxis with procaine penicillin, 600,000 units intramuscularly, and kanamycin, 0.2 g intramuscularly, was begun preoperatively and continued, once daily, for 6 days. The thorax was opened through the fourth left intercostal space using sterile surgical technique. A balloon occluder developed by Barger[14] (Hazen Everett Co., Mahwah, New Jersey) was placed about the left anterior descending coronary artery, at the level of the tip of the left atrial appendage, or about the left circumflex coronary artery, 1 to 3 cm from its origin. Teflon®-coated stainless steel wires, to be used to record a bipolar atrial electrogram, unipolar electrograms from the future ischemic and nonischemic ventricle and the precordial electrocardiogram, were sutured in place. The inflation tubing for the occlusive balloon and the recording electrodes were externalized through skin buttons between the scapulas, and the wound was closed. Experiments were not performed until at least 10 days after operation, at which time the dogs had fully recovered.

Experimental procedure: The experimental environment was designed to isolate the animal from the investigator and the recording equipment. The animal was completely isolated visually, but complete auditory and olfactory isolation was not attempted. Each dog was allowed to become accustomed to the environment through repeated exposure to it. The electrode wires and pressure tubing attached to the implanted equipment and to the plastic connectors located between the scapulas were led out of the dog's cage through a hollow leash. The electrocardiogram and electrograms were recorded on an Electronics for Medicine, DR-12 recorder and Hewlett-Packard 3944 magnetic recording system. Constant pressure for inflating the occlusive balloon was provided from an H-tank containing air through a Matheson 1-H line regulator. Pressure sufficient to stop coronary flow was determined in acute experiments, and, in one dog, 2 weeks after implantation of the occluder with use of a chronically implanted Biotronex flow probe.

Approximately 45 minutes after the animal had been placed in the experimental environment, the first occlusion was begun. The electrocardiogram and electrogram were recorded continuously before, during and after occlusion. The occlusion was continued until one of the four criteria for termination of an occlusion had been satisfied: (1) The occlusion had lasted a predetermined period; this period was 3.5 to 5.5 minutes for different animals and was constant for each sequence of occlusions. (2) Two or more ventricular premature depolarizations occurred in sequence. (3) At least three ventricular premature beats occurred within 15 seconds. (4) Any ventricular beats occurred within the first 75 seconds of occlusion.

Each occlusion was performed as part of a sequence of three: (1) control, (2) intervention, and (3) control. An interval of 1 to 3 days was allowed after drug trials to permit complete elimination of drugs before the next occlusion.

The effect of an intervention on arrhythmias was evaluated by comparing the results of the intervention trial with the results of the preceding and subsequent control occlusions. Trials of tolamolol and UM-272, as part of a sequence of three occlusions, were performed in random order. With repeated occlusions the time from the onset of occlusion to the occurrence of the first ventricular premature beats often increased until occlusions lasted for 5.5 minutes without ventricular arrhythmia. When ventricular premature beats ceased to occur during control occlusions, a behavioral stress was added to the control environment, and drug trials were continued with the stressful environment replacing the original control environment. In subsequent sequences of occlusions the effect of a drug in the stressful environment was compared with the effect of the stressful environment alone. We studied the effects of drug administered intravenously 45 minutes before occlusion. The drugs and doses used were tolamolol, 0.25 to 2.3 mg/kg*; UM-272, 4.5 to 5.3 mg/kg†; and diazepam, 0.5 to 10 mg/kg.

Several forms of behavioral stress were used. In one form, the animal was taken into a laboratory with which it was not familiar, and the occlusion was performed in the unfamiliar environment. Alternatively, a stressful stimulus was administered at regular intervals before and during the occlusion. The stressful stimulus was either a light, followed 10 seconds later by a sudden noise, or a noise, followed 10 seconds later by a subcutaneous electrical shock. The intensity of the stimuli was sufficient to cause an arousal or a startle response but never sufficient to cause vocalization or evidence of pain. The timing and intensity of the stimulus were constant throughout any sequence of occlusion.

* Provided by Dr. Colin Taylor of Pfizer Pharmaceuticals.
† Provided by Dr. Richard Dean of G. D. Searle and Co.

Data analysis: Sequences comparing control occlusions with intervention trials were rejected before data analysis if they failed to meet two criteria: (1) Ventricular premature beats must have occurred during at least two occlusions of the sequence; and (2) ventricular premature beats must not have occurred during control electrocardiographic records taken before or more than 10 seconds after release of an occlusion, except when an occlusion was terminated by ventricular fibrillation.

The latency of an occlusion was defined as the time, in seconds, from the onset of the occlusion until the first ventricular premature beat or until release of occlusion if no ventricular premature beat occurred. The effect of an intervention on latency was measured as the difference between the intervention latency and the average control latency and expressed as a percent of the average control latency. The significance of changes in latency was evaluated by a paired Student's *t* test and Wilcoxin's rank sum test for paired data. In general, we anticipated that if an intervention induced arrhythmias sooner after the onset of occlusion (that is, latency decreased), the severity of the arrhythmias would increase, whereas if the appearance of arrhythmias was delayed (that is, latency increased), then the severity of the arrhythmias would decrease.

The grade of an occlusion was defined as a function of the change in the electrocardiogram with time after the onset of the occlusion. The grade of an occlusion was zero from the onset of the occlusion until the occurrence of the first ventricular premature depolarization. An occlusion was assigned grade 1 when at least one premature beat had occurred and all premature beats that had occurred had followed a sinus beat. Grade 2 indicated that two premature beats, but no more than two, had occurred in sequence. Grade 3 indicated that three or more premature beats had occurred in sequence, but ventricular fibrillation had not occurred. Grade 4 indicated the occurrence of ventricular fibrillation.

The effect of heart rate on latency was evaluated for all animals with data from at least three control occlusions during which ventricular premature beats had occurred. For each animal, the control occlusion with the longest latency was designated the heart rate standard. The elevation in heart rate above the heart rate standard was computed for each 10 second interval from the onset of occlusion. The mean of these differences was taken as a measure of heart rate for each occlusion. For each dog, the correlation coefficient between the mean elevation in heart rate and the latency was computed. The mean correlation coefficient and the statistical significance of the correlation coefficients were determined as described by Fisher.[18] The effect of each intervention on the mean elevation of heart rate also was determined.

Results

Thirty-four sequences of three occlusions (control, intervention, control) were obtained from 12 dogs. Three sequences were discarded because no ventricular premature beats occurred during the second and third occlusions. Four sequences were discarded because of the presence of premature beats in control records taken before, or more than 10 seconds after, release of the occlusions. Twenty-seven of 34 sequences were analyzed to determine the effect of the interventions.

In the absence of coronary occlusion, stress did not precipitate arrhythmias in any animal, except for a single isolated premature beat, in Dog E, on its first exposure to the noise stimulus. This did not recur on any subsequent exposure to the sound stimulus in the absence of coronary occlusion.

TABLE I

Effects of Stress on Latency in Five Dogs

Dog	Occlusion*	Latency (sec)	% Change
E	C	212	...
	S(N)	99	−57
	C	251	...
	S(N)	164	−35
	S(N)	136	...
	C	209	...
F	C	167	...
	S(ES)	241	+3
	C	301	...
H	C	330	...
	S(ES)	151	−50
	C	274	...
I	C	315	...
	S(Env)	204	−35
	C	315	...
J	C	330	...
	S(ES)	230	−30
	C	330	...
Mean ± SEM	...	...	−34 ± 8.5†

* In all five dogs the left circumflex coronary artery was occluded.

† Probability (*P*) value <0.02, *t* test; *P* <0.05, Wilcoxin rank sum test.

C = control occlusion; Env = strange environment; ES = electric shock; N = noise; S = occlusion under stress; SEM = standard error of the mean.

Changes in Latency

Occlusions without pharmacologic interventions: The effect of stress: Four or more control occlusions were obtained for each of nine dogs. There was considerable variability in latency for most animals. Eight animals (Dogs A to D and H to K) were subjected to three or more control occlusions before the introduction of stress. Dogs I, J and K showed irregular but progressive prolongation of latency during the initial control occlusions. The first two dogs studied, Dogs A and B, initially were tested before complete recovery from operation as judged by clinical criteria (5 and 7 days postoperatively). For subsequent occlusions they appeared to have recovered fully. After full recovery from operation both showed a gradual but irregular prolongation of latency. No animals showed progressive decreases in latency before the introduction of stress.

Six sequences involving stress (a control occlusion, an occlusion under stress and a control occlusion) were obtained for five animals (Table I). For one sequence stress consisted of performing the occlusion in an unfamiliar environment (Dog I); for one (Dog E) the stress was a loud noise; and for three dogs (Dogs F, H and J) it was a subcutaneous shock. In five of six sequences, stress decreased latency markedly with respect to the preceding and following control occlusions. Under stress, latency decreased by 34 ± 8 percent (mean ± standard error of the mean) (probability [*P*] <0.02, *t* test; *P* <0.05, Wilcoxin's rank sum test). In Dog H, on the post-stress control trial, heart rate was increased by atrial pacing, to maintain the rate 5 to 10 beats/min higher than the rate during the occlusion under stress. Under stress, the first premature beat occurred after 151 seconds. No premature beats occurred

during either of the control occlusions, which lasted 330 and 274 seconds, respectively.

Effects of pharmacologic interventions: *The effects of tolamolol* on latency were evaluated for six dogs (Table II); in each case a complete sequence permitted comparison of the effect of tolamolol on latency with latency during prior and succeeding control occlusions. For five of the six tests tolamolol increased latency above both control values for the animal (Fig. 1, Table II). In one dog (Dog D) latency increased from a control value of 156 to 211 seconds with tolamolol but, on the succeeding control occlusions, increased further to 276 seconds. Overall, latency increased after administration of tolamolol by 26 ± 7 percent ($P < 0.02$, t test; $P < 0.05$, Wilcoxin's rank sum test).

Six sequences evaluating the effects of UM-272 were obtained for six dogs (Table III, Fig. 1). For three sequences the

TABLE II

Effect of Tolamolol (T) on Latency in Six Dogs

Dog	Dose (mg/kg)	Occlusion*	Latency (sec)	% Change
A	0.25	C	126	+37
		T	214	
		C	187	
C	0.25	C	122	
		T	179	+36
		C	141	
D	0.25	C	156	
		T	211	−2
		C	276	
H	2.5	C	240	
		T	330	+40
		C	232	
J	0.7	C	231	
		T	330	+33
		C	264	
K	0.9	C	98	
		T	119	+12
		C	115	
Mean ± SEM				+26.0 ± 7†

* In Dogs A, C and D the left anterior descending coronary artery was occluded; in Dogs H, J and K the left circumflex coronary artery was occluded.

† P value > 0.02, t test; < 0.05 Wilcoxin rank sum test.

Symbols and conventions as in Table I.

TABLE III

Effect of UM-272 (UM) on Latency in Six Dogs

Dog	Dose (mg/kg)	Occlusion*	Latency (sec)	% Change
A	5.0	C	144	
		UM	136	−23
		C	210	
B	4.3	C	217	
		UM	259	+14
		C	239	
H	5.0	C, S	241	
		UM, S	54	−75
		C, S	212	
I	5.0	C, S	256	
		UM, S	58	−71
		C, S	150	
J	5.0	C, S	193	
		UM, S	220	+5
		C, S	228	
K	5.3	C	104	
		UM	93	−19
		C	127	
Mean ± SEM				−28 ± 15†

* In Dogs A and B the left anterior descending coronary artery was occluded; in Dogs H, I, J and K the left circumflex coronary artery was occluded.

† $0.1 < P < 0.05$, t test; $P < 0.1$, Wilcoxin rank sum test.

Symbols and conventions as for Table I except that S indicates that the control and drug tests were performed with the animal under the influence of stress.

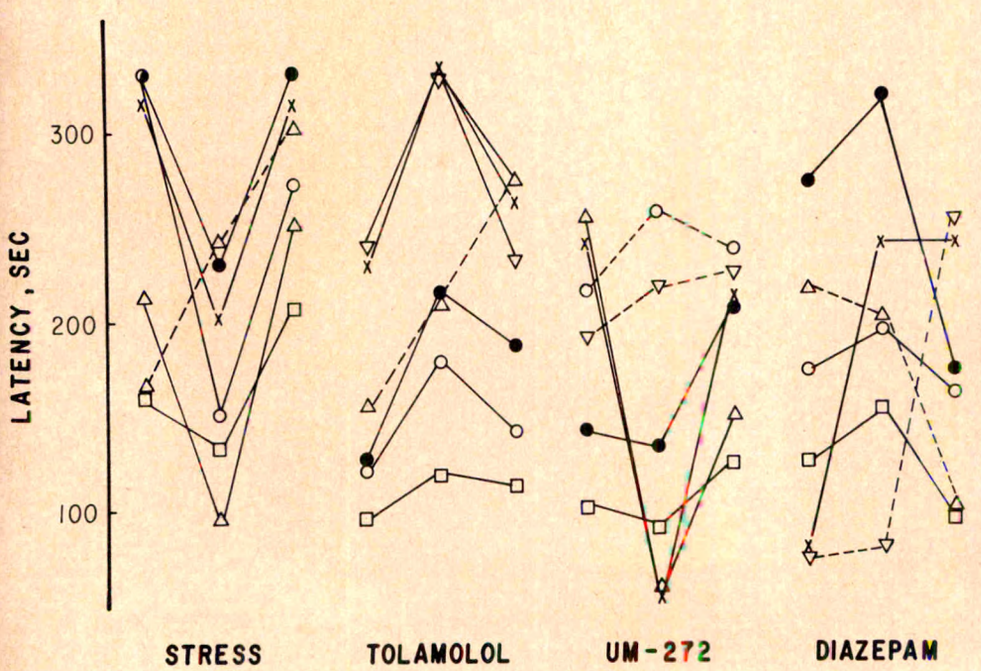


FIGURE 1. Effects of each intervention on latency for all sequences of occlusions. Latency is measured on the **vertical axis. Each line connecting three points** represents a sequence of occlusions. The point at the **left** and **right ends** of the line represent, respectively, the latency of the pre- and postintervention control occlusion. The point in the **middle** of each line, where the angle is, represents the latency of the intervention trial. Clearly, stress decreased latency and tolamolol increased it.

effects of UM-272 and stress were compared with the effects of the identical stress alone. In the absence of applied stress, UM-272 changed latency by −75, −71 and +5 percent. Although for two of three comparisons of latency after UM-272 with control latency there was a clear decrease, and for two of three comparisons of stressed latency after UM-272 with latency during the same stress there was a large decrease, for all six sequences the mean change in latency caused by UM-272 (−28 ± 15 percent) was not significant. Nevertheless, it was clear that UM-272, an antiarrhythmic agent with predominant direct cardiac effect, did not prolong latency in either type of test. Thus the effect of UM-272 on latency was significantly different from that of tolamolol ($P < 0.01$, t test).

Six sequences evaluating the effects of diazepam were performed in five dogs (Table IV). Four compared latency after diazepam with control latency, and two compared the effect of diazepam plus stress with the effect of stress alone. Overall, for the experiments in which the effects of diazepam on latency were compared with the average control values for the same animals, the drug caused a consistent increase ranging from 17 to 43 percent. For one animal (Dog I) the control latencies before and after the test with diazepam differed markedly (217 and 99 seconds, respectively), and thus the calculated prolongation due to diazepam is of questionable significance. For the two dogs used to evaluate the effects of diazepam on latency during stress, the pre- and post-drug values for latency during stress were too variable to permit evaluation of drug effect on latency. Figure 1 and Table V summarize the effects of the interventions with stress and drugs.

Changes in Grade

The effect of the several interventions on grade is shown in Figures 2 to 4. For each sequence, the grade of each occlusion is plotted as a function of time. It is clear from Figure 2 that for five of the six animals stress caused the grade to exceed zero at an earlier time after occlusion than during the control test and also that, during stress, a higher grade was obtained in five of six animals. Ventricular fibrillation and ventricular tachycardia did not occur during any of the control occlusions but were present in two of seven occlusions with stress. In summary, for five of six sequences in which the effect of stress was compared with the control data, the grade of the stressed occlusion was greater than or equal to the control grade at all times during occlusion.

The effects of tolamolol on grade are shown for complete sequences for six dogs in Figure 3. For four animals (Dogs A, H, J and K) the highest grade attained during occlusion after administration of tolamolol was less than the highest grade for either of the two control occlusions for the same animal, even though the occlusion after drug administration lasted longer than one or both of the control tests. In two animals (Dogs H and J) given tolamolol there were no arrhythmias after occlusions lasting over 5 minutes, and in one (Dog K) that manifested ventricular fibrillation in both control tests, after tolamolol there was only ventricular tachycardia occurring at a later time. Therefore, stress increased grade at any given time in these experiments, whereas tolamolol tended to decrease grade. With UM-272, there was an increase in grade in three of six trials (Fig. 4), and with diazepam there was a decrease in grade in two of six trials and an increased grade in 1 of 6 trials (Fig. 5).

TABLE IV

Effects of Diazepam (D) on Latency in Five Dogs

Dog	Drug Dose (mg/kg)	Occlusion*	Latency (sec)	% Change
D	10.0	C	276	
		D	320	+43
		C	173	
G	8.0	C	175	
		D	197	+17
		C	162	
H	1.4	C, S	78	
		D, S	241	+51
		C, S	241	
I	7.0	C	217	
		D	201	+27
		C	99	
	1.0	C, S	79	
		D, S	80	−52
		C, S	256	
K	0.53	C	127	
		D	154	+38
		C	98	
Mean ± SEM				+21 ±38†

* In all five dogs, the left circumflex coronary artery was occluded.
† Difference not significant.
Symbols and conventions as in Table III.

Electrocardiographic Characteristics

Clearly it would have been helpful if we had been able to quantify the degree of ischemia caused by each occlusion in each animal. Because we could not, we attempted to evaluate the similarity, rate and magnitude of change in the electrocardiogram and ventricular electrogram for each occlusion. The sequence of changes in the J point and the S-T segment and the changes in the T wave were remarkably similar for successive occlusions in any dog as were the changes in the unipolar electrogram recorded from the ischemic segment of the ventricle. For occlusions with short latency the sequence of changes in electrocardiographic wave form occurred more rapidly; for occlusions with long latency, the sequence of changes occurred more slowly. It was possible in any dog to determine the correlation between the latency and the time from the onset of occlusion to an arbitrary and easily identifiable point in the sequence of changes in the electrocardiographic wave form that occurred during the occlusion. The average correlation coefficient, among all dogs, was 0.7, and was significantly greater than 0 ($P < 0.02$).

We also studied the relation between the prematurity of the ventricular beats and the subsequent rhythm by measuring the coupling coefficient of the ventricular beats. This was the ratio of the coupling interval to the Q-T interval for premature beats that followed a sinus beat. The coupling

TABLE V

Effect of Intervention on Latency of Arrhythmia

Intervention	% Change*	*P* Value: *t* Test	*P* Value: Wilcoxin Rank Sum test
Stress	−34 ± 8	<0.02	<0.05
UM-272	−28 ± 15	NS	NS
Diazepam	21 ± 15	NS	NS
Tolamolol	26 ± 7	<0.02	<0.05

* Mean ± standard error of the mean.
NS = not significant; *P* = probability.

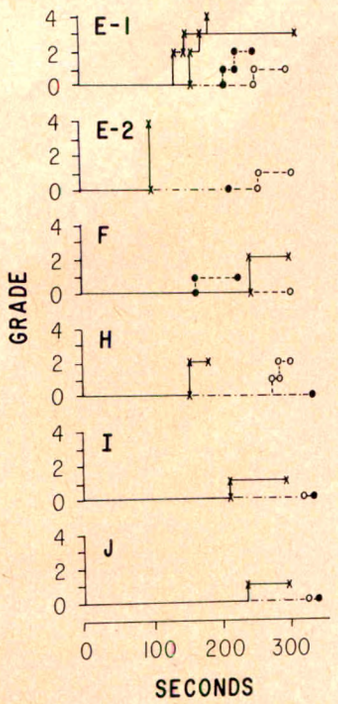


FIGURE 2. Dogs E, F, H, I and J. Grade as a function of time for each occlusion, in each sequence, in which stress was the intervention. Each sequence is shown on a separate set of axes. Grade is indicated on each vertical axis and time on the horizontal axis. The intervention trial (x——x) and each control trial (O——O, ●——●) are shown for each sequence.

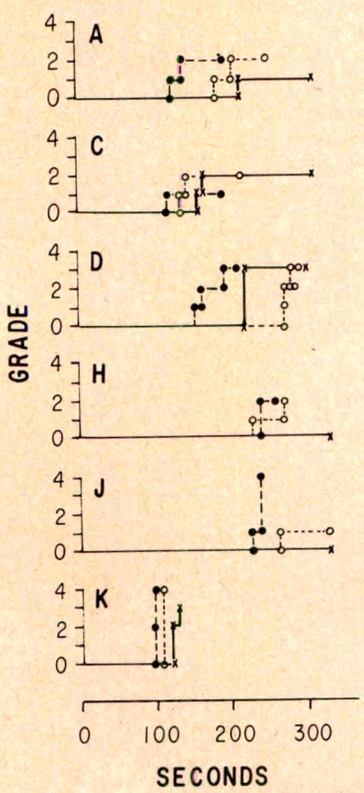


FIGURE 3. Dogs A, C, D, H, J and K. Grade as a function of time for each occlusion, in each sequence, in which tolamol was the intervention. Conventions as in Figure 2 except that tolamolol replaces stress as the intervention.

coefficient for isolated ventricular beats ranged from 1.0 to 2.1; that for ventricular beats initiating a run of ectopic impulses ranged from 0.9 to 2.0 and that for ventricular beats initiating fibrillation from 1.0 to 1.6. Although there was considerable overlap in the ranges, the mean coupling coefficients were 1.16 ± 0.17 for ventricular beats followed by fibrillation, 1.27 ± 0.28 for ventricular beats initiating runs of ectopic activity and 1.38 ± 0.24 for isolated ventricular beats. The mean values for the first two classes were significantly less (P <0.02 and 0.05, respectively, t test) than for the third. Ventricular beats with coupling coefficients less than 1.0 were rare; we recorded only three, and all three initiated runs of ventricular beats. These data might be influenced by an association between higher heart rates and shorter coupling coefficients; we analyzed the data for each dog and found no indication of a significant relation between heart rate and coupling coefficient.

Other Variables

Heart rate: We determined the correlation coefficients between latency and the mean elevation of heart rate for nine dogs as described under Methods. The correlation coefficients ranged from +0.48 to −0.86. For three dogs, the correlation coefficient was significantly different from 0. In these three dogs, it was negative. The average correlation coefficient for all dogs was −0.532 and was significantly less than 0 (P <0.01). Thus, on the average, as heart rate increased, latency decreased.

The effect of each intervention on the mean elevation of heart rate also was evaluated. Stress increased the mean el-

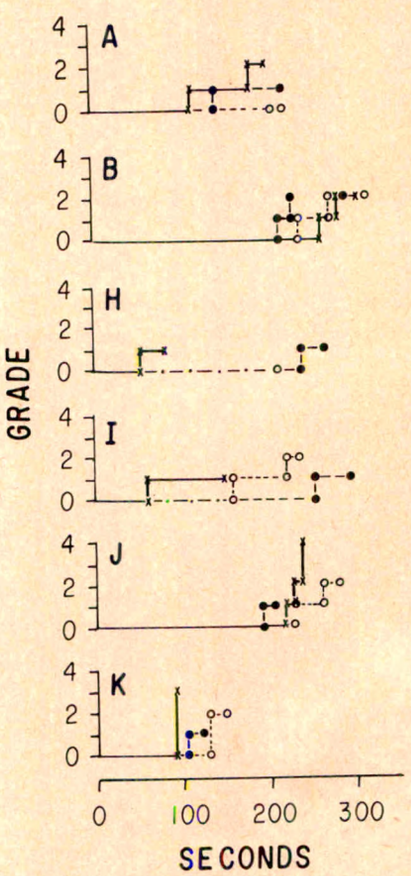


FIGURE 4. Dogs A, B, H, I, J and K. Conventions as in Figure 2 except that UM-272 replaces stress as the intervention.

evation of heart rate by 24 ± 10 beats/min. Tolamolol decreased the mean elevation of heart rate by 17 ± 7 beats/min. UM-272 changed the mean elevation of heart rate + 8 ± 6 beats/min; and diazepam changed the mean elevation of heart rate by − 2 ± 8 beats/min.

Doses: Logarithmic dose versus response curves were plotted for diazepam and tolamolol, and no clear relation between dose and magnitude of response was evident for either drug.

Discussion

Mechanisms involved in arrhythmias after coronary occlusion: In the dog model we have used, arrhythmias consistently develop soon after coronary occlusion, and these arrhythmias appear to be similar to those that are thought to cause sudden death in patients with coronary artery disease. In our model, stress increased the severity of the arrhythmias and shortened the time from onset of occlusion to their appearance. Beta adrenergic blockade had the opposite effect, as did diazepam in the more stable preparations. The possible mechanisms for these effects are complex and numerous. It seems clear that there is an association between the level of sympathetic activity and the likelihood of early and severe arrhythmias. In part this depends on differences in heart rate, but other mechanisms may be involved.

The electrophysiologic and metabolic changes that occur in an ischemic area of the ventricle and are thought to underlie arrhythmias have recently been reviewed.[19,20] During ischemia there is a loss of resting transmembrane potential, automaticity is enhanced and slow responses are likely to occur. Norepinephrine is known to enhance automaticity and to increase the likelihood of slow responses of the sort that can lead to reentrant excitation. An earlier study[21] showed that during ischemia caused by ligation of the left anterior descending coronary artery electrograms recorded from the ischemic zone undergo changes that might well result from loss of resting potential and propagation of the slow response. Electrographic amplitude decreased markedly, complexes widened and became polyphasic and activity was progressively delayed until it persisted throughout the T wave. Thus one might assume that stress increases the likelihood of severe arrhythmias not only by increasing the disparity between blood flow and metabolic requirement but also through the liberation of norepinephrine, directly augmenting several arrhythmogenic mechanisms. Beta adrenergic blockade would be expected to antagonize both of these types of effects of stress and did so. This finding is in agreement with data from randomized prospective studies in man[22–24] that demonstrated a probable protective effect of beta blockade against sudden death. The actions we have shown for diazepam are more difficult to analyze. This agent may, through its behavioral effects, have reduced the physiologic consequences of stress. It may also have acted by some of its more direct effects on the cardiovascular system such as those on coronary and peripheral resistance.[25]

Tolamolol (a beta blocking agent) versus UM-272 (a local anesthetic antiarrhythmic agent): We hoped to compare the actions of tolamolol, a beta adrenergic blocking drug that was almost devoid of direct myocardial depressant effects, with an agent that caused no beta blockade but did exert actions typical of a local anesthetic antiarrhythmic agent. We chose this pair of agents to try to evaluate the possibility that typical local anesthetic antiarrhythmic drugs may actually increase the likelihood of severe arrhythmias after the onset of myocardial ischemia. This would occur because the intensity of their action is dependent on extracell potassium concentration $[K^+]_0$. It has been shown for lidocaine, procainamide and quinidine[26,27] that the extent to which a given concentration of drug impairs the ability of a myocardial cell to develop a normal action potential upstroke increases as $[K^+]_0$ increases. This appears to result from more intense blockade of the so-called fast sodium channel.[28] During ischemia, potassium leaks out of the cells and the extracell concentration of drug in the myocardium that was nontoxic might become toxic in the ischemic areas as $[K^+]_0$ increases. The more intense depressant effects might then lead to impaired conduction, unidirectional block and arrhythmia. The findings comparing results for dogs given UM-272 with results during control occlusions, both with and without stress, are not conclusive but at least demonstrate no protection against arrhythmias by UM-272 and suggest that the hypothesis probably deserves further evaluation.

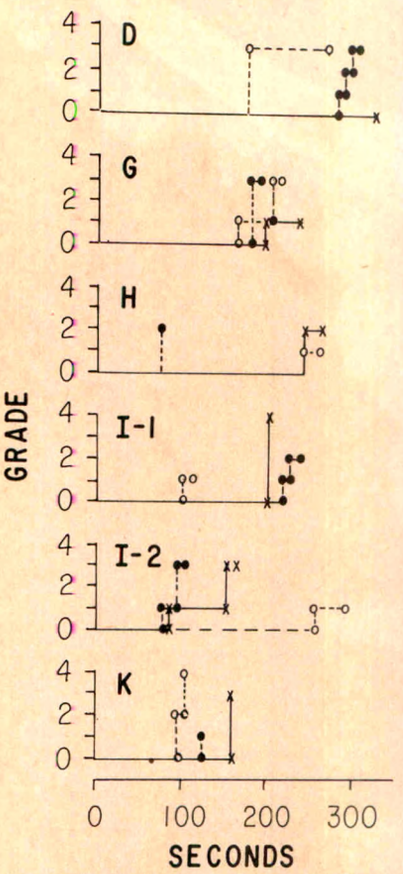


FIGURE 5. Dogs D, G, H, I and K. Conventions as in Figure 2 except that diazepam replaces stress as the intervention.

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Relations Between Ventricular Refractoriness and Regional Myocardial Blood Flow After Acute Coronary Occlusion

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Myocardial ischemia has been associated with dispersion of ventricular refractory periods and this dispersion has been related to the ventricular arrhythmias seen with coronary occlusion. This study relates the degree of change in measured ventricular refractory period with the degree of regional myocardial blood flow abnormality after coronary occlusion. When regional myocardial blood flow is less than 70 percent of that of nonischemic areas, refractory periods are significantly ($P < 0.001$) shortened. The greatest change in refractory periods occurs in areas with a regional myocardial blood flow that is 21 to 40 percent of that of nonischemic areas. Marked (less than 20 percent) and minimal (61 to 80 percent) reductions in regional myocardial blood flow are associated with less, but still significant, shortening of ventricular refractory periods. Thus dispersion of refractoriness can be related to the inhomogeneity of regional myocardial blood flow after acute coronary occlusion. Interventions designed to salvage ischemic myocardium by increasing regional myocardial blood flow may affect dispersion of ventricular refractory periods in complex and divergent ways.

Acute coronary occlusion is associated with electrophysiologic changes and ventricular arrhythmias, presumably as a result of decreased regional myocardial blood flow. The electrophysiologic changes believed to be related to the genesis of ventricular arrhythmias include dispersion of ventricular refractoriness[1–6] as well as slow conduction.[6–12] However, relations between the degree of reduction of regional myocardial blood flow and the corresponding regional electrophysiologic changes have not been delineated.

This study was designed to establish the relations between regional myocardial blood flow and a regional electrophysiologic characteristic, ventricular refractoriness. Thus, ventricular refractory periods were determined in subendocardial and subepicardial layers of ischemic and nonischemic ventricular myocardium, and regional myocardial blood flow was measured in the same sites. A correlation could then be made between the degree of change in ventricular refractoriness, the degree of reduction of regional myocardial blood flow and the transmyocardial location of a myocardial sample.

Methods

Experimental procedure: Seventeen mongrel dogs were anesthetized with a chloralose-urethane mixture (30 mg/kg body weight of chloralose and 300 mg/kg of urethane) and ventilated with room air using a Harvard respirator. A catheter was placed in the femoral artery for recording blood pressure, monitoring arterial blood gases and obtaining reference blood samples for flow determinations. The heart was exposed through a median sternotomy. After sinus nodal crush, pacing from the right atrial appendage at a cycle length of 450 or 400 msec was established. A polyethylene tube was placed in the left atrial appendage for administration of radioactive microspheres.

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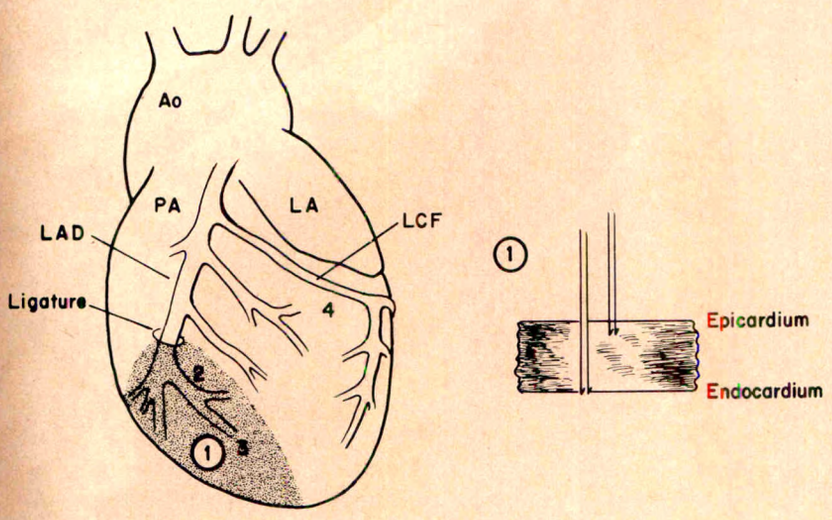


FIGURE 1. Schematic diagram of a typical experiment demonstrating the site of left anterior descending coronary artery (LAD) occlusion above the last major diagonal branch and the resultant area of ischemia **(stippled).** Site 1 is a central ischemic area, containing subendocardial and subepicardial bipolar plunge wire electrodes placed as illustrated in the insert. Sites 2 and 3 are border ischemic areas, also containing bipolar electrodes placed in the same fashion as site 1. Site 4 is a nonischemic area in the distribution of the circumflex artery (LCF) that also contains similarly placed bipolar plunge wire electrodes. Ao = aorta; LA = left atrium; PA = pulmonary artery.

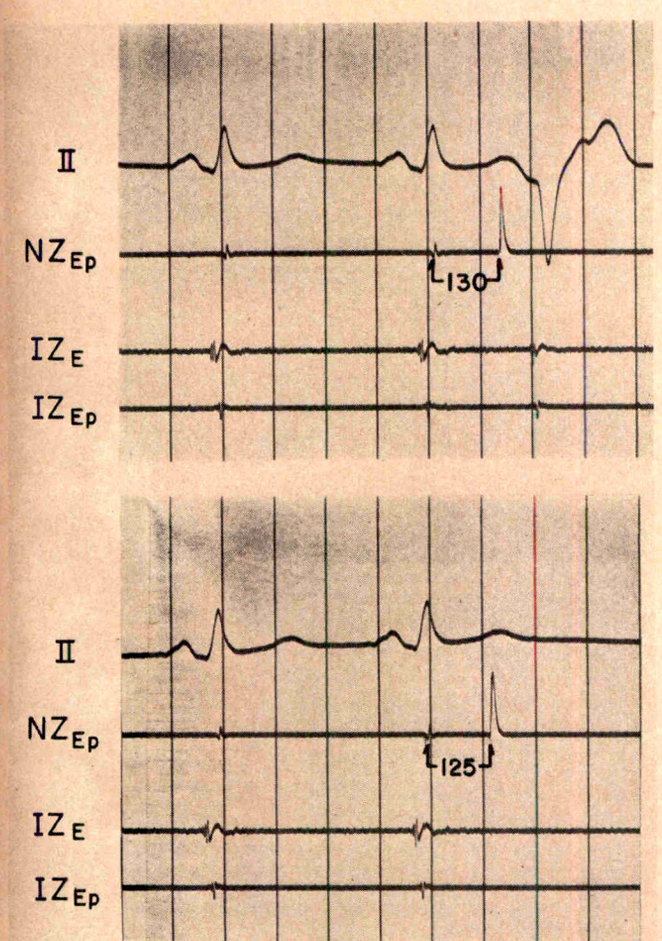


FIGURE 2. Recordings of electrocardiographic lead II (II) and bipolar electrograms from the nonischemic zone epicardium (NZ_{Ep}) and from the endocardium (IZ_E) and epicardium (IZ_{Ep}) of the ischemic zone. Time lines indicate 100 msec. **Top panel,** a stimulus is delivered to the nonischemic zone epicardium 130 msec after the preceding local electrogram and results in a conducted response. **Bottom panel,** a stimulus delivered 5 msec earlier results in failure to capture the ventricle. The refractory period of the nonischemic zone epicardium therefore is 125 msec.

Using limited dissection the anterior descending coronary artery was exposed and a snare placed around it just proximal to the last major diagonal branch. The resultant zone of ischemia was estimated by observing the area of cyanosis and dyskinetic contraction that developed with a 15 to 30 second occlusion at this site. Four areas (Fig. 1) were then chosen to represent (1) an area from the center of the potentially ischemic zone; (2 and 3) two areas from the periphery of, but falling within, the potentially ischemic zone, and (4) a control nonischemic area in the distribution of the circumflex artery. Teflon®-coated plunge wire electrodes (interelectrode distance 1 to 2 mm were then placed in the subendocardial and subepicardial layers of each area. The subendocardial and subepicardial placement of these electrodes was visually confirmed at the conclusion of each experiment. Thus, bipolar electrograms were recorded from a total of eight sites (four subendocardial, four subepicardial) in each animal.

Refractory period determinations: Using a programmable stimulator (WP Instruments, New Haven, Connecticut), we performed refractory period determinations by introducing a premature ventricular stimulus coupled to the last of a series of eight atrial paced beats progressively earlier in diastole until the stimulus failed to capture the ventricle. The ventricular refractory period was defined as the longest interval at which a ventricular stimulus failed to capture the ventricle. This interval was measured for each site from the local bipolar electrogram to the stimulus artifact that was delivered to the same bipolar electrode (Fig. 2). The atrial paced cycle length was either 400 or 450 msec and remained constant during each experiment. Because ischemia is known to increase the threshold for pacing an average of 8- to 10-fold,[13,14] a stimulus strength was selected that was 10 to 15 times diastolic threshold (approximately 3 milliamperes) determined in the control state. This then resulted in a stimulus strength of approximately two times diastolic threshold in the ischemic area, and stimulation strength was not varied during the experiment. Ischemic segments occasionally became refractory to ventricular stimulation, and these segments were discarded from further analysis.

Control refractory period determinations at each of the eight segments were performed 1 hour after placement of the plunge wire electrode to ensure stabilization after the surgical manipulation. After control measurements, the snare was tightened to produce a total continuous occlusion of the an-

terior descending artery. Refractory period determinations were repeated at each of the eight segments at 5 and 15 minutes and every 30 minutes until 180 minutes after continuous occlusion. During each refractory period determination, recordings were made at a paper speed of 100 mm/sec of standard electrocardiographic lead II and the bipolar electrograms were filtered between 40 and 500 hertz. Because of differences in the control values for the refractory period between segments in single experiments and among experiments, changes in refractory periods were expressed as a percent of their control value. No medications other than anesthesia were administered during the course of these experiments.

Myocardial blood flow measurements: Regional myocardial blood flow was measured using the radioactive microsphere technique.[15–18] Commercially available, radioactively labeled (strontium-85, cesium-141 and chromium-51) microspheres (15 ± 5 μ) were injected into the left atrium 2 minutes, 1 hour and 3 hours, respectively, after continuous occlusion of the left anterior descending coronary artery. Microspheres were suspended in dextran (a drop of Tween 80® was added to each vial) and were thoroughly agitated in an ultrasonic bath before injection. The syringe containing the microspheres was also vigorously shaken before injection. Each injection contained approximately 1.1 to 2.7 · 10^6 microspheres. With use of a Harvard withdrawal pump, a reference arterial blood sample (30 cc) was obtained over a 2 minute period starting immediately before injection of the microspheres. This sample was then divided into 10 aliquots (3 cc each) for counting.

Transmyocardial samples of ischemic and nonischemic areas: After completion of each experiment the dog was killed and the heart removed from the thorax. The atria, right ventricle and interventricular septum were removed and epicardial fat and major blood vessels trimmed from the left ventricle. Transmyocardial samples (average weight 1 g) were taken at the site of each of the four pairs of plunge wire electrodes. Thus, electrophysiologic and blood flow determinations were available for the same endocardial and epicardial segments. In addition, two transmyocardial samples bordering each of the ischemic areas and four transmyocardial samples bordering the nonischemic area were taken. These samples served as checks for the reliability of blood flow determination.

Each transmyocardial sample was then divided into endocardial and epicardial halves. The tissue samples were weighed and placed in plastic vials and counted in a well counter at each of three different energy windows (strontium-85, 460 to 560 kev; chromium-51, 300 to 400 kev; cesium-141, 120 to 170 kev). With appropriate corrections,[19] the radioactivity of each radionuclide was obtained and expressed as a ratio of counts/g in the ischemic sample (endocardial, epicardial and transmural) to counts/g in the average of the five nonischemic samples (endocardial, epicardial and transmural, respectively). Absolute blood flow was also calculated as follows: Flow (cc/min per g) = counts/g in tissue sample divided by counts/min per cc in reference blood samples.

Controls: Three animals underwent the same protocol except that no occlusion of the left anterior descending coronary artery was performed. Thus these animals served as sham-operated controls.

All data were analyzed using the Student's group t test.

Results

Regional Myocardial Blood Flow

Flow determinations in the three sham-operated dogs demonstrated that there was no difference between flow to myocardial segments that contained the electrodes and flow to surrounding segments that did not contain the electrodes.

In the 17 dogs with coronary occlusion, flow determinations at 2 minutes, 1 hour and 3 hours were not significantly different in either ischemic or nonischemic areas. Thus flow data are expressed as averages of these three values. For nonischemic myocardium average blood flow levels were as follows: endocardial 1.2 cc/min per g (range 0.9 to 1.6); epicardial 1.1 cc/min per g (range 0.9 to 1.5); and transmural 1.2 cc/min per g (range 0.9 to 1.5). These values correlate well with those found by other investigators.[15–18]

In potentially ischemic areas the spectrum of transmural flow reduction was wide and ranged from marked (2 percent of nonischemic transmural flow) to absent (119 percent of nonischemic transmural flow). Endocardial flow was always more markedly reduced than epicardial flow in any area with reduced transmural flow. The heterogeneity of flow in the ischemic area was evident: Thus, some endocardial segments with endocardial flow less than 20 percent of nonischemic endocardial flow were adjacent both to epicardial segments with similarly low epicardial flow (hence transmural flow was also less than 20 percent of nonischemic transmural flow) and to epicardial segments with epicardial flow greater than 81 percent of nonischemic epicardial flow (hence transmural flow was approximately 50 percent of nonischemic transmural flow). This heterogeneity has been demonstrated previously.[18] Because of this heterogeneity, segments were separated according to their transmural flow (less than 20 percent, 20 to 70 percent and greater than 71 percent of nonischemic transmural flow) and then further categorized according to endocardial or epicardial flow as a percent of nonischemic endocardial or epicardial flow, respectively.

No infarct produced was large enough to cause significant changes in systemic arterial pressure or arterial blood gases during the course of the experiment. Spontaneous ventricular fibrillation did not occur.

Refractory Period Determinations

In the three sham-operated animals, refractory period determinations were remarkably constant. Small fluctuations of 5 to 10 msec did occur but were of similar magnitude and in the same direction in all segments. Therefore refractory period changes in the ischemic samples were corrected for the small fluctuations seen in the nonischemic sample during the experimental period. Thus, the changes expressed represent a dispersion of refractoriness from nonischemic areas.

In the ischemic zone, refractory periods shortened by as much as 35 percent of control values. The maximal changes in refractory periods were invariably seen within the first 60 minutes after occlusion and usually significantly earlier. These changes are similar in magnitude to those reported by others.[1–5,14]

The time course of change in refractory periods was quite variable, but a minimal plateau value was achieved in most instances. The maximal percent change from

control value was therefore taken for each endocardial or epicardial segment, thus allowing for comparison among the entire group of 17 animals.

Overall relation between transmural flow and maximal change in refractory period (Fig. 3 to 5): When transmural flow was less than 70 percent of nonischemic transmural flow, refractory periods were significantly (P <0.001) shorter than when transmural flow was greater than 70 percent of nonischemic transmural flow (Fig. 3). Thus when an endocardial or epicardial segment was part of a transmyocardial segment with a transmural flow less than 70 percent of nonischemic transmural flow, its refractory period was significantly changed, regardless of the individual endocardial or epicardial flow.

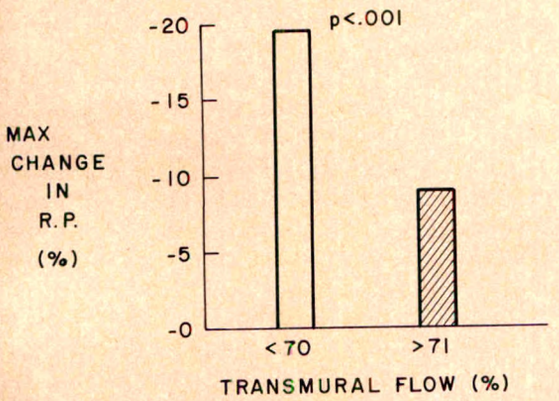


FIGURE 3. Refractory period (R.P.) changes in all segments as a function of transmural myocardial blood flow. When a segment was part of a transmural segment with transmural flow less than 70 percent of nonischemic transmural flow, highly significant (probability [p] value <0.001) changes in refractory periods occurred. See text for discussion. MAX = maximal.

Within this overall framework of transmural flow, several variations occurred (Fig. 4). When transmural flow was less than 20 percent of nonischemic transmural flow, endocardial segments changed significantly less (P <0.05) than epicardial segments. In addition, refractory periods in these segments (transmural and endocardial flow less than 20 percent of nonischemic transmural or endocardial flow, respectively changed significantly less (P <0.005) than those of segments with similar endocardial flow (less than 20 percent of nonischemic endocardial flow) but transmural flow 21 to 70 percent of nonischemic transmural flow. These endocardial samples (endocardial and transmural flow less than 20 percent of nonischemic endocardial and transmural flow, respectively) still had refractory periods significantly (P <0.05) shorter than those of nonischemic samples.

The greatest changes in refractory periods were seen in segments in which transmural flow was 21 to 70 percent of nonischemic transmural flow and endocardial or epicardial flow 21 to 40 percent of nonischemic endocardial or epicardial flow, respectively (Fig. 5). Among segments with transmural flow 21 to 70 percent of nonischemic transmural flow, there was a tendency to a linear relation between the degree of reduction in endocardial or epicardial flow and the change in refractory periods (Fig. 5). The differences between these groups achieved statistical significance only when the group with endocardial and epicardial flow values 21 to 40 percent of nonischemic endocardial or epicardial flow were compared with the group in which these values were more than 81 percent of the nonischemic level.

The effect of reduction in transmural flow is particularly demonstrated by epicardial segments with epicardial flow greater than 81 percent of nonischemic epicardial flow. Figure 6 demonstrates that when transmural flow was less than 70 percent of nonischemic

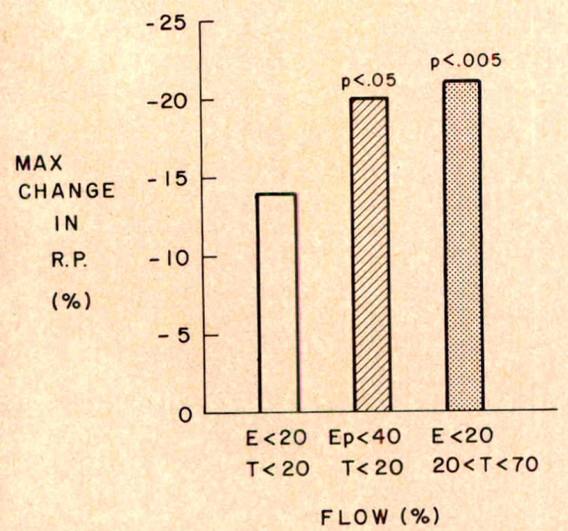


FIGURE 4. Refractory period (R.P.) changes in all segments with marked reduction of regional blood flow. Probability (p) values refer to differences in comparison with endocardial segments with both endocardial (E) and transmural (T) flow less than 20 percent of nonischemic endocardial or transmural flow, respectively **(white bar).** See text for discussion. Ep = epicardial; MAX = maximal.

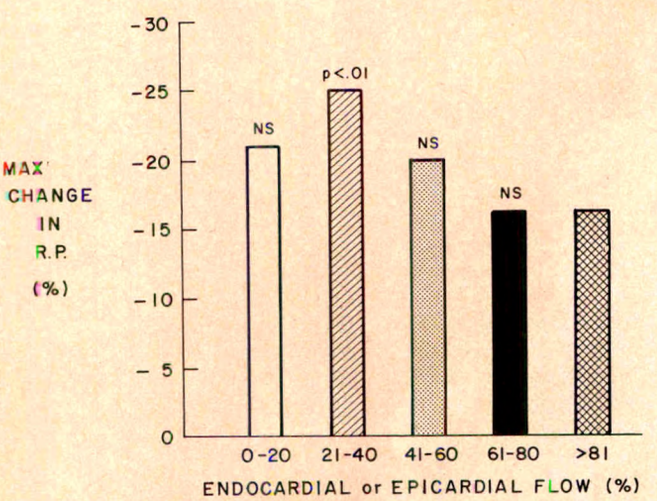


FIGURE 5. Refractory period (R.P.) changes in all segments with transmural flow 21 to 70 percent of nonischemic transmural flow. Probability (p) values refer to differences in comparison with segments with epicardial flow greater than 81 percent of nonischemic epicardial blood flow **(bar 5).** See text for discussion. MAX = maximal; NS = not significant.

transmural flow, epicardial segments of such transmural samples showed significantly shorter (P <0.005) refractory periods than epicardial segments with similar epicardial flow (greater than 81 percent of nonischemic epicardial flow) but transmural flow greater than 70 percent of nonischemic transmural flow.

Discussion

Electrophysiologic changes induced by myocardial ischemia have been extensively investigated using several approaches.[1–12] Han and Moe[1] demonstrated that myocardium made acutely ischemic displayed considerable dispersion of refractoriness in a circumscribed area. This dispersion contributes to a milieu that may predispose to or produce ventricular arrhythmias. Several investigators[2–5] later confirmed this dispersion of refractoriness after coronary occlusion and used it as a model for studying antiarrhythmic agents.

In a different approach, other investigators[7,12] demonstrated that bipolar electrograms become fragmented and prolonged in areas of acute ischemia. This fragmentation and prolongation may represent slow conduction of an impulse over a circuitous pathway. Boineau and Cox[8] demonstrated sufficient temporal delay of activation to suggest that slow conduction is responsible for the genesis of reentrant ventricular beats in acutely ischemic myocardium. Scherlag et al.[11] demonstrated a close temporal relation between prolonged epicardial activation and the occurrence of ventricular arrhythmias. It was further demonstrated[12] that spontaneous cessation of ventricular tachycardia was invariably associated with a progressive decrease in delay of activation time whereas the progression of ventricular tachycardia to fibrillation was associated with a progressive increase in the delay of epicardial activation.

Although electrophysiologic changes that may predispose to ventricular arrhythmias have been demonstrated after coronary occlusion, the relations of these changes to the degree of regional myocardial blood flow reduction has not been established. In our study we chose to examine the changes in a regional electrophysiologic characteristic, ventricular refractoriness, with changes in regional myocardial blood flow. Changes in the transmyocardial (that is, endocardial or epicardial) and radial distribution of blood flow and in the refractory period were studied.

Possible limitations of method: An inherent limitation in making these correlations is the inevitable mismatch between the size of the myocardial sample required for radioactive microsphere flow determination and that required for refractory period determination. Heterogeneity of refractory periods[1] and of blood flow[18] is a known feature of coronary occlusion. Accurate flow determinations with the microsphere technique require the delivery of an adequate number of microspheres to a myocardial sample so that count rates are reliable. To obtain reliable count rates in the ischemic zone, myocardial samples in the range of 0.5 g were required. Within a sample of this size, considerable heterogeneity of flow undoubtedly occurs and, as Han and Moe[1] showed, ventricular refractoriness may vary significantly. Theoretically, therefore, our model may not be optimally sensitive to a potential relation between regional myocardial blood flow and changes in refractory period.

Ischemia is known to increase the diastolic threshold for ventricular stimulation to an average of 8 to 10 times the diastolic threshold in the nonischemic ventricle.[13,14] This increase in pacing threshold was accommodated for in our experiments by performing refractory period determinations at 10 to 15 times the nonischemic diastolic threshold during both the control and ischemic states. With use of this stimulus strength, nonischemic refractory periods did not change during the experimental period. This stimulus strength resulted in a stimulus strength of approximately twice diastolic threshold in ischemic areas. Some ischemic areas became refractory to stimulation entirely and were discarded from data analysis. The changes we demonstrated with this stimulus strength in refractory periods of the ischemic zone are in close accord in both direction and magnitude with those reported by others[2–5,14] Any error introduced by this technique would result in underestimation of the shortening of ischemic zone refractory periods and thus would also tend to obscure a relation between blood flow and changes in refractory period.

Relations between transmural blood flow and refractory periods: In spite of these theoretical limitations, several significant relations were demonstrated. The predominant association with changes in refractory periods seems to be a reduction in transmural blood flow. When transmural flow was less than 70 percent of nonischemic tramsmural flow, significant shortening of ventricular refractory periods in both subendocardial and subepicardial layers was consistently seen. The association of the refractory period changes with transmural flow reduction to less than 70 percent of nonischemic transmural flow correlates well with the demonstration of metabolic changes occurring at similar

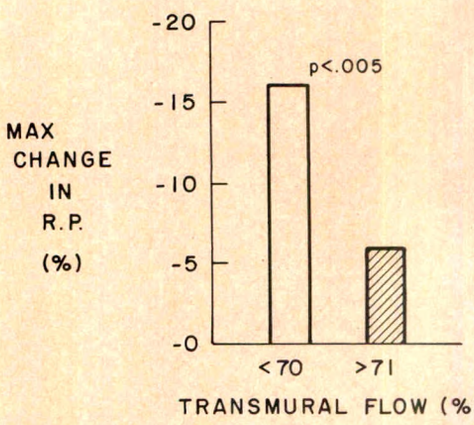


FIGURE 6. Refractory period (R.P.) changes in epicardial segments with preserved epicardial flow (more than 81 percent of nonischemic epicardial flow). In spite of preserved epicardial flow, when transmural flow was reduced significant (probability [p] <0.005) shortening of the refractory period of epicardial segments occurred. See text for discussion.

levels of flow reduction.[20] In addition to the relation between transmural flow reduction and changes in ventricular refractory period, several other significant relations emerged.

Maximal reduction of transmural flow (less than 20 percent of nonischemic transmural flow) was associated with several interesting features. Endocardial segments in this transmural flow distribution demonstrated significantly less change in refractory periods than was observed in epicardial segments in the same transmural flow distribution ($P < 0.05$) or in endocardial segments with similar endocardial flow (less than 20 percent of nonischemic endocardial flow) but transmural flow greater than 21 percent of nonischemic transmural flow (Fig. 4). Thus there may be dispersion of refractory period changes in a transmyocardial distribution in the center of an infarct as well as a radial distribution in the endocardial layer of an infarct.

In areas of significant, but not maximal, transmural flow reduction (21 to 70 percent of nonischemic transmural flow), there was a tendency to a linear relation of increasing change in refractoriness to decreasing endocardial or epicardial blood flow (Fig. 5). This tendency did not extend to endocardial flow less than 20 percent of nonischemic endocardial flow, and statistical significance was achieved only for segments with endocardial or epicardial flow 21 to 40 percent of nonischemic endocardial or epicardial flow, respectively. Thus, a gradient of change in refractoriness may also occur in a radial distribution within the infarct area.

Epicardial segments with relatively well preserved epicardial blood flow (greater than 80 percent of nonischemic epicardial flow) still showed a significant shortening of refractory period when transmural flow to those areas was less than 70 percent of nonischemic transmural flow (Fig. 6). This relation may be a result of using a relatively strong stimulus strength in areas with intermingling of normal and ischemic myocardium, but it still demonstrates that significant dispersion of refractoriness occurs in the epicardial layer at the border of an infarct and normal area. Changes in refractoriness in these epicardial segments may also result from factors other than reduced blood flow, such as changes in wall tension or stretch or metabolites released from adjacent ischemic areas.

Clinical implications: We have demonstrated that significant dispersion of refractoriness occurs in a transmyocardial and radial distribution within an area of infarction as well as between the infarcted area and normal myocardium and that this dispersion may result from the inhomogeneity of blood flow within the infarcted area. Potential sites of origin of ventricular arrhythmias may therefore be dependent on and predictable from regional myocardial blood flow. The effects of antiarrhythmic agents may also be dependent on regional myocardial blood flow, because of both the potential sites of origin of ventricular arrhythmias and the dependence on regional blood flow for delivery of antiarrhythmic agents to these sites. Interventions directed at salvaging ischemic myocardium by increasing regional myocardial blood flow could have complex and divergent electrophysiologic effects depending on their effect on central versus peripheral areas of the infarction. Our results provide a basis for assessing the dependence on regional myocardial blood flow for therapeutic effectiveness of antiarrhythmic agents as well as for assessing the electrophysiologic effects of interventions directed at salvaging ischemic myocardium.

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Catheter Recording of Bachmann's Bundle Activation From the Right Pulmonary Artery: A New Technique for Atrial Mapping and the Study of Supraventricular Tachycardia

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The feasibility of recording electrograms from the region of Bachmann's bundle was studied in 16 open chest dogs by means of an electrode catheter introduced into the proximal right pulmonary artery under fluoroscopy. Confirmatory electrograms from Bachmann's bundle and the high right atrium were directly obtained with close bipolar plunge wire electrodes. In all 16 dogs, it was possible to record atrial electrograms from the right pulmonary arterial catheter. The onset of right pulmonary arterial electrograms consistently coincided with the peak of Bachmann's bundle electrograms in nine dogs and was within 10 msec in seven dogs during pacing of the sinus node, left atrium and right ventricle. Furthermore, pacing from the right pulmonary arterial catheter produced the earliest atrial activation in Bachmann's bundle. During direct pacing of Bachmann's bundle, the right pulmonary arterial electrogram preceded all other atrial recording sites. During sinus nodal pacing, the right pulmonary arterial electrogram was inscribed 5 to 25 msec after the high right atrial electrogram, within 20 msec of the low atrial septal electrogram and 15 to 45 msec ahead of the low left atrial electrogram. During right ventricular pacing the low right atrial septal activation preceded the right pulmonary arterial electrogram by 5 to 35 msec, and the latter was inscribed 10 to 25 msec before the high right atrium. Bachmann's bundle reentry beats induced by the extrastimulus method in 12 dogs could be successfully distinguished from sinus or atrioventricular nodal reentry by the inscription of right pulmonary arterial electrograms.

Preliminary results in four patients studied indicate that it is possible to record from the proximal right pulmonary artery electrograms of good quality that reflect activation from the region of Bachmann's bundle. It is concluded that the right pulmonary arterial catheter electrode provides a reliable technique for (1) recording an atrial electrogram from the region of Bachmann's bundle, (2) identifying the precise mechanism of supraventricular tachycardia, and (3) evaluating interatrial conduction.

Localization of the site of reentry during supraventricular tachycardia has heretofore been based on criteria that are currently under review.[1] These criteria, namely, similarity of the P wave configuration to that of the sinus beat and a "high to low" right atrial activation sequence, were considered essential in identifying sinus nodal reentry.[2] In addition, the diagnosis of atrioventricular (A-V) nodal reentry was based on the presence of negative P waves in leads II, III and aVF, with a "low to high" right atrial activation sequence.[2]

However, recent studies[3–5] have shown these criteria to be inadequate for precise localization of the region of reentry. It has become clear that the configuration and axis of the P wave are unreliable indicators of the origin of atrial activation. Goodman et al.[6] reported that positive ret-

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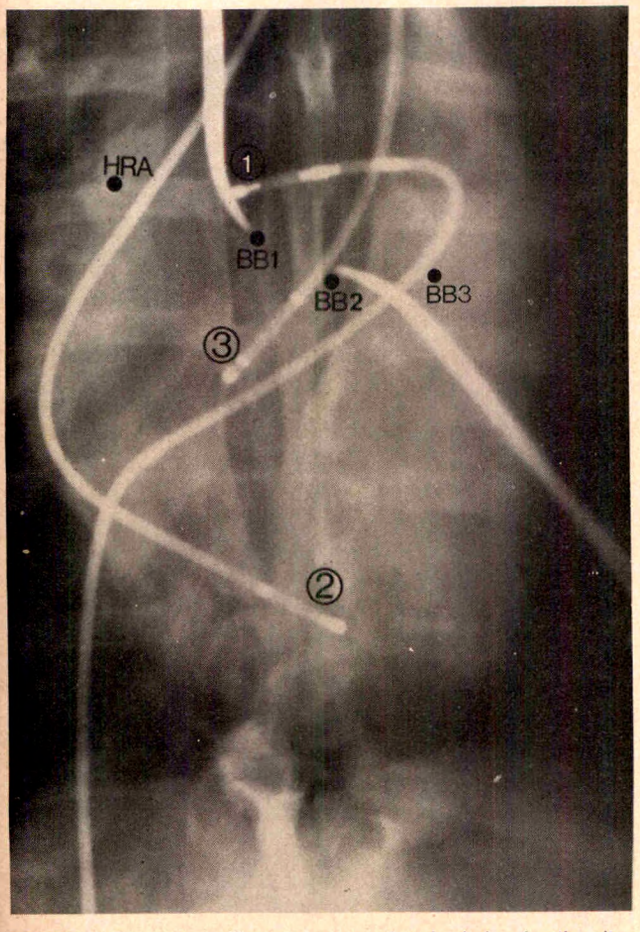


FIGURE 1. Chest X-ray film (anteroposterior view) showing the sites of recording electrograms used in a canine experiment. One catheter (1) is in the right pulmonary artery, another (2) in the distal coronary sinus and a third (3) in the posterior aortic sinus. The three **closed circles** indicate the positions of the plunge wire electrodes impaled in the high right atrium (HRA), close to the sinus node, and in two portions of Bachmann's bundle (BB1 and BB2). The latter two electrodes are indicated by tips of the surgical hemostats. BB3 = junction of body and appendage of left atrium, corresponding to the terminal portion of Bachmann's bundle.

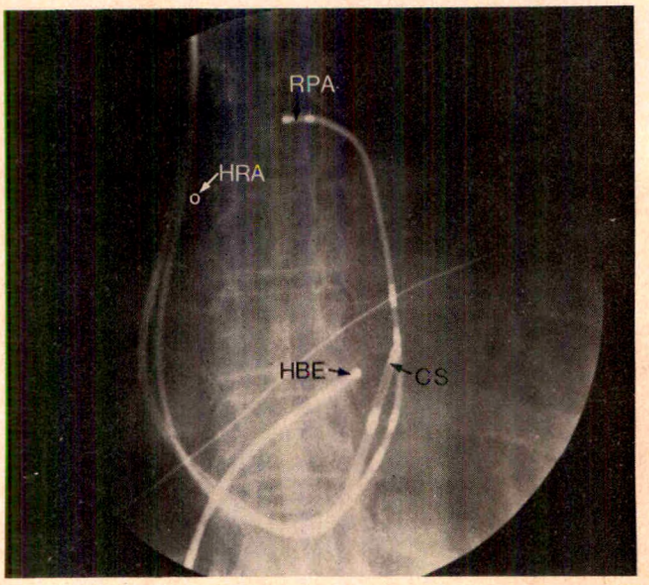


FIGURE 2. Chest X-ray film from a patient. One catheter was advanced into the right pulmonary artery (RPA) to record Bachmann's bundle electrogram after recording high right atrial activation (HRA). CS = distal coronary sinus catheter; HBE = His bundle electrode catheter.

rograde P waves in leads II, III and aVF could result from rapid spread of excitation through the atrial septum to Bachmann's bundle. Waldo et al.[7,8] emphasized that the determinant of P wave contour is not the site of impulse formation but rather the timing of Bachmann's bundle activation and the direction of impulse spread through Bachmann's bundle. Furthermore, the "high to low" or "low to high" right atrial activation sequence cannot distinguish sinus or A-V nodal reentry from intraatrial reentry, including reentry within the region of Bachmann's bundle. Recent experimental studies[9] suggested that reentry in the region of Bachmann's bundle could not be identified from other mechanisms of supraventricular tachycardia without recording atrial electrograms from Bachmann's bundle.

The precise identification of Bachmann's bundle activation utilizing an intraatrial catheter electrode may not be valid because of the lack of obvious anatomic landmarks. Because the right pulmonary artery lies on the superior wall of the left atrium, and is anatomically close to Bachmann's bundle,[9] we studied the feasibility of recording electrograms from the region of Bachmann's bundle using an electrode catheter positioned in the right pulmonary artery. This study also examined the significance of right pulmonary arterial electrograms in the diagnosis of supraventricular tachycardia.

Methods

Canine experiments: Sixteen healthy adult mongrel dogs (weight 17 to 23 kg) were anesthetized with sodium pentobarbital (30 mg/kg body weight), intubated and ventilated with a Harvard respirator using room air. The heart was exposed with a mid sternal incision and suspended in a pericardial cradle. A bipolar or tripolar electrode catheter (Elecath no. 7) with an interelectrode distance of 10 or 1 mm was advanced into the right pulmonary artery from the femoral vein under fluoroscopy with the tip of the catheter located approximately in the mid line of the mediastinal shadow (Fig. 1, position 1). Confirmatory electrograms from Bachmann's bundle (BB1, the portion overlying the atrial septum, and BB2, the left atrial portion approximately 10 mm apart from BB1) were directly obtained with close bipolar plunge wire electrodes (indicated by the tips of the surgical hemostats in Fig. 1). Activation from the terminal portion of Bachmann's bundle was also recorded at the junction of the left atrial body and the left atrial appendage in five experiments (BB3). An additional plunge wire electrode was impaled in the high right atrium close to the sinus node (HRA in Fig. 1). Two other electrode catheters (interelectrode distance of 1 or 10 mm) were introduced into the distal coronary sinus and the posterior aortic sinus to record low left atrial activation and His bundle electrograms with low atrial septal activation, respectively.

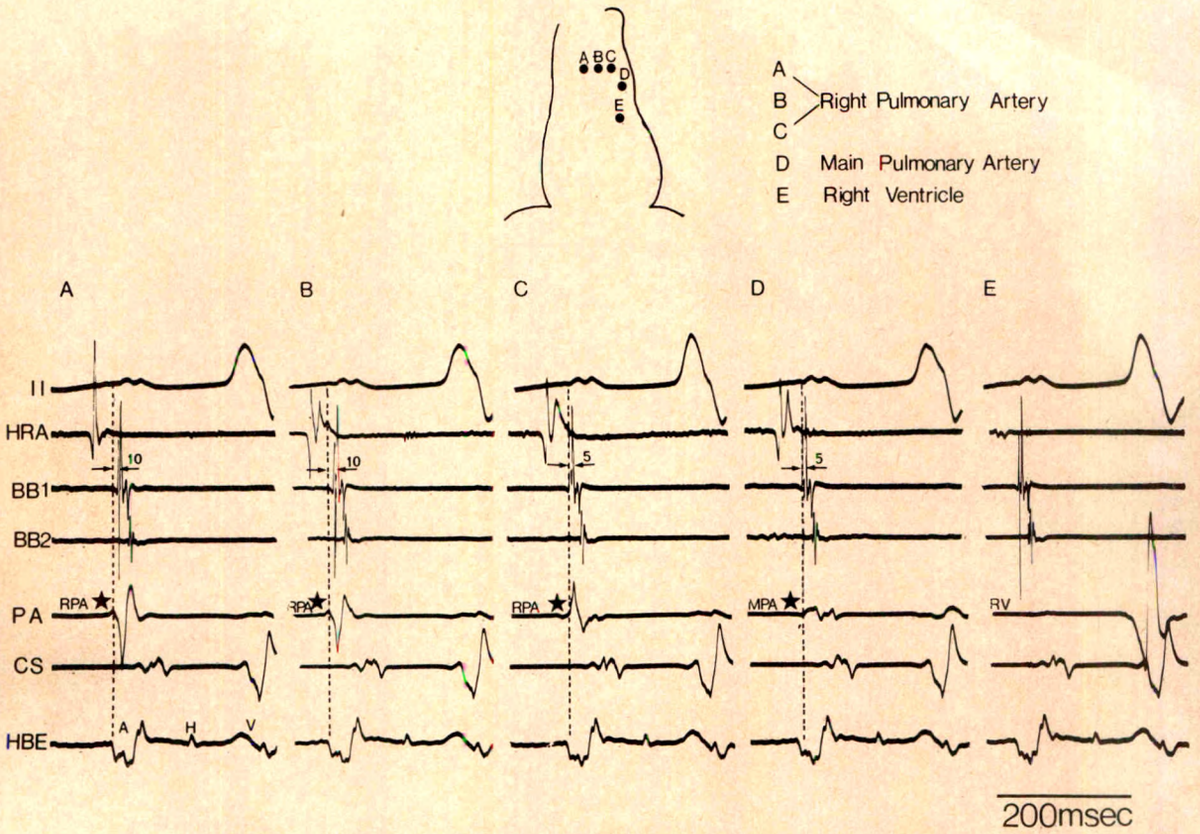


FIGURE 3. Schematic illustration of the catheter positions (**top**) and corresponding atrial electrograms (**bottom**). The right pulmonary arterial (RPA) catheter (catheter 1 in Fig. 1) was pulled back from position A to position E (right ventricular outflow tract). The electrograms from the high right atrium (HRA) and Bachmann's bundle (BB1 and BB2) were obtained with plunge wire electrodes. The coronary sinus (CS) and His bundle (HBE) electrograms were recorded with catheters 2 and 3 of Figure 1. The **dotted lines** represent the onset of electrograms recorded in the pulmonary artery (PA, **stars**). MPA = main pulmonary artery; RV = right ventricle; II = lead II of the surface electrocardiogram.

The heart was driven by a unipolar pacing electrode impaled in (1) the sinus node, (2) the high left atrium (approximately 10 mm apart from the BB2 electrode or close to the BB3 electrode), and (3) the right ventricle. Filtered 50 to 1,000 hertz electrograms were recorded simultaneously with a lead II electrocardiogram on a multichannel recorder (Hewlett-Packard 4578A) at a paper speed of 200 mm/sec, or on a memory oscilloscope (Tektronics 5115) at a sweep speed of 500 mm/sec.

The onset of rapid deflection of the right pulmonary arterial electrogram was compared with the peak of the Bachmann's bundle electrograms obtained with close bipolar plunge wire electrodes (BB1 and BB2) during (1) sinus rhythm or sinus nodal pacing, (2) high left atrial pacing, and (3) right ventricular pacing at a constant rate. To verify further the right pulmonary arterial electrogram, the right pulmonary artery was stimulated through the same electrode catheter at the site where the recording was made, and the atrial activation sequence was evaluated.

Right pulmonary arterial electrograms were also recorded in 12 dogs during Bachmann's bundle reentry arrhythmias. To facilitate the induction of atrial reentry, the extrastimulus technique and a known atrial depressant, aprindine 4 mg/kg intravenously, were utilized according to previously described methods.[9–11] Bachmann's bundle reentry was diagnosed when all three of the following criteria[9] were satisfied: (1) repetitive induction of reentry arrhythmias by critically timed premature stimuli, (2) demonstration of the earliest site of atrial activation at either BB1, BB2 or BB3, and (3) demonstration of fragmentation or delay in the Bachmann's bundle electrograms during the inscription of a premature complex.

Human studies: The feasibility of recording from the right pulmonary arterial catheter electrode was also investigated in four patients referred for electrophysiologic studies. After informed consent was obtained, the patients were studied in the postabsorptive state. The electrode catheter with an interelectrode distance of 10 mm was advanced into the right pulmonary artery from a right antecubital vein. The catheter tip was positioned approximately in the mid line of the mediastinal shadow and directed inferiorly against the arterial wall (Fig. 2). Simultaneous recording of the His bundle electrogram or distal coronary sinus electrogram was used as a reference electrode. A standard electrocardiogram and filtered 40 to 500 hertz intracavitary electrograms were recorded simultaneously on a multichannel oscilloscopic recorder (Electronics for Medicine DR-8) at a paper speed of 100 or 200 mm/sec.

Results

Canine Studies

Atrial electrograms from the right pulmonary artery: Figure 1 shows the proximity of the tip of the right pulmonary arterial catheter to the BB1 electrode, as indicated by the tip of a surgical hemostat on an X-ray film in the anteroposterior view. Atrial electrograms were successfully obtained in all experiments at the proximal portion of the right pulmonary

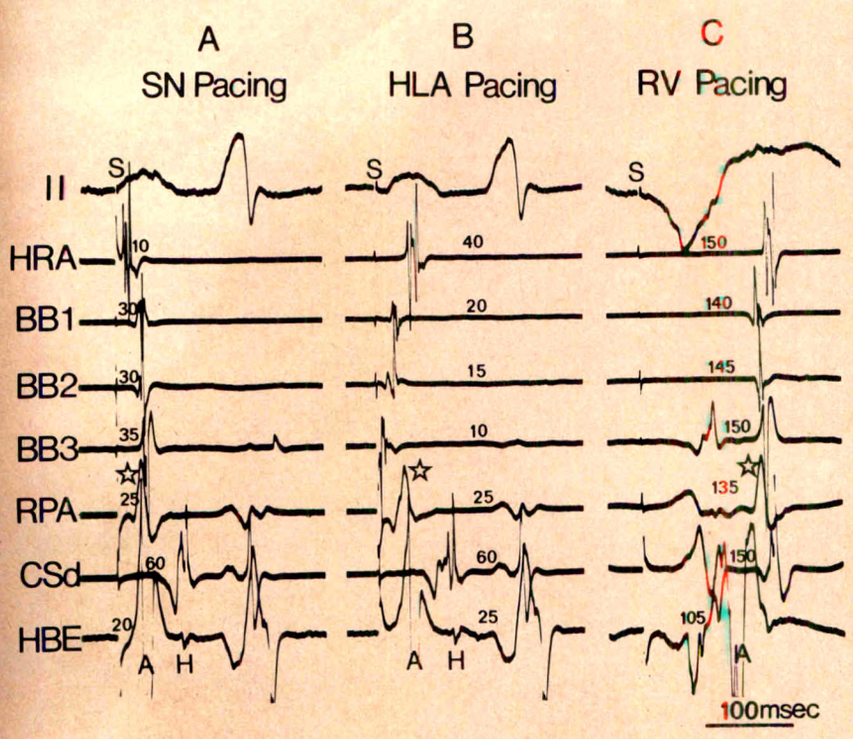


FIGURE 4. Relation between the Bachmann's bundle electrogram and the right pulmonary arterial (RPA) electrogram during pacing of (**A**) the sinus node (SN), (**B**) the high left atrium (HLA) and (**C**) the right ventricle (RV). The right pulmonary arterial electrogram was inscribed within 5 msec of the BB1 electrogram in each tracing. A = low atrial septal activation recorded in the His bundle electrogram; BB = Bachmann's bundle; CSd = distal coronary sinus; H = His bundle activation; HBE = His bundle electrogram; HRA = high right atrium; S = pacing stimulus; II = lead II of the surface electrocardiogram.

artery. Figure 3 shows the sequential tracings recorded during gradual pullback of the catheter from the right pulmonary artery to the right ventricular outlfow tract. A single electrogram, often biphasic, was obtained within the right pulmonary artery (areas A, B and C) 2 to 3 cm away from the main pulmonary artery. Although the configuration of the right pulmonary arterial electrograms during sinus rhythm varied slightly with different catheter positions (indicated by stars in Fig. 3, A to C), the timing of the electrograms appeared to be fairly constant in relation to the BB1 electrograms. The atrial electrogram gradually disappeared as the catheter was withdrawn to the main pulmonary artery (position D) and the right ventricle (position E).

During sinus nodal pacing, the onset of the right pulmonary arterial electrograms consistently coincided with the peak of the BB1 electrogram in nine dogs and was inscribed 5 to 10 msec before or after the BB1 electrograms in seven dogs (Fig. 4A, star). During high left atrial pacing (close to the BB3 electrode), the right pulmonary arterial electrogram was also inscribed within 10 msec before or after the BB1 electrogram. In an example shown in Figure 4B, the right pulmonary arterial electrogram was inscribed 5 msec after the BB1 electrogram. In five dogs in which the catheter was positioned in the right pulmonary artery close to the main pulmonary artery, the right pulmonary arterial activation occurred simultaneously with the BB2 or BB3 electrograms (not shown). Retrograde atrial activation sequence could be studied in seven dogs with right ventricular pacing (Fig. 4C); again a close correlation of the right pulmonary arterial electrogram with the BB1 electrogram was observed. The right pulmonary arterial electrogram preceded the BB1 electrogram by 5 msec (135 msec versus 140 msec in Fig. 4C).

Activation sequence during pacing of the sinus node and right ventricle: *During sinus nodal pacing* (Fig. 4A and 5, top left panel), the high right atrium was the initial site of atrial activation in all experiments. The right pulmonary arterial deflection was inscribed 5 to 25 msec after the high right atrial electrogram, and 15 to 45 msec before the low left atrial electrogram obtained with the coronary sinus catheter. Low atrial septal activation recorded on the His bundle electrogram occurred simultaneously with the right pulmonary arterial activation in 6 dogs, and within 20 msec of the latter in 10 dogs.

During right ventricular pacing the low atrial septum was consistently the earliest site of activation in all seven dogs (Fig. 4C). The right pulmonary arterial electrogram was inscribed 5 to 35 msec after the low atrial septal electrogram, and 10 to 30 msec before the high right atrial electrogram. In an example shown in Figure 4C, the right pulmonary arterial electrogram was inscribed 30 msec after the electrogram of the low atrial septum and preceded that of the high right atrium by 15 msec.

Right pulmonary artery pacing: Figure 5 illustrates the tracings recorded from another experiment at a sweep speed of 500 mm/sec in which right pulmonary arterial pacing was performed. The right pulmonary arterial electrogram was again shown in close relation to the Bachmann's bundle electrograms (BB1 and BB2) and was inscribed after the BB1 electrogram by 3 and 9 msec during sinus nodal and high left atrial pacing, respectively (Fig. 5, top panel). To validate further the right pulmonary arterial electrode, the right pulmonary artery and Bachmann's bundle (BB1) were stimulated with each recording electrode. In Figure 5, left lower panel, pacing from the right pulmonary artery captured the atria and produced the earliest atrial activation in the area of the BB1 electrode (small arrow). Although there was a delay of 18 msec between the pacing spike and the BB1 electrogram, the BB1 electrogram (small arrow) clearly preceded the other atrial electrograms. Furthermore, direct pacing from Bachmann's bundle, using the BB1 electrode (Fig. 5, right lower panel) resulted in the earliest atrial activation of the right pulmonary arterial electrogram (small arrow). Also note the similar atrial activation sequence observed during pacing of the right pulmonary artery and the BB1 electrode.

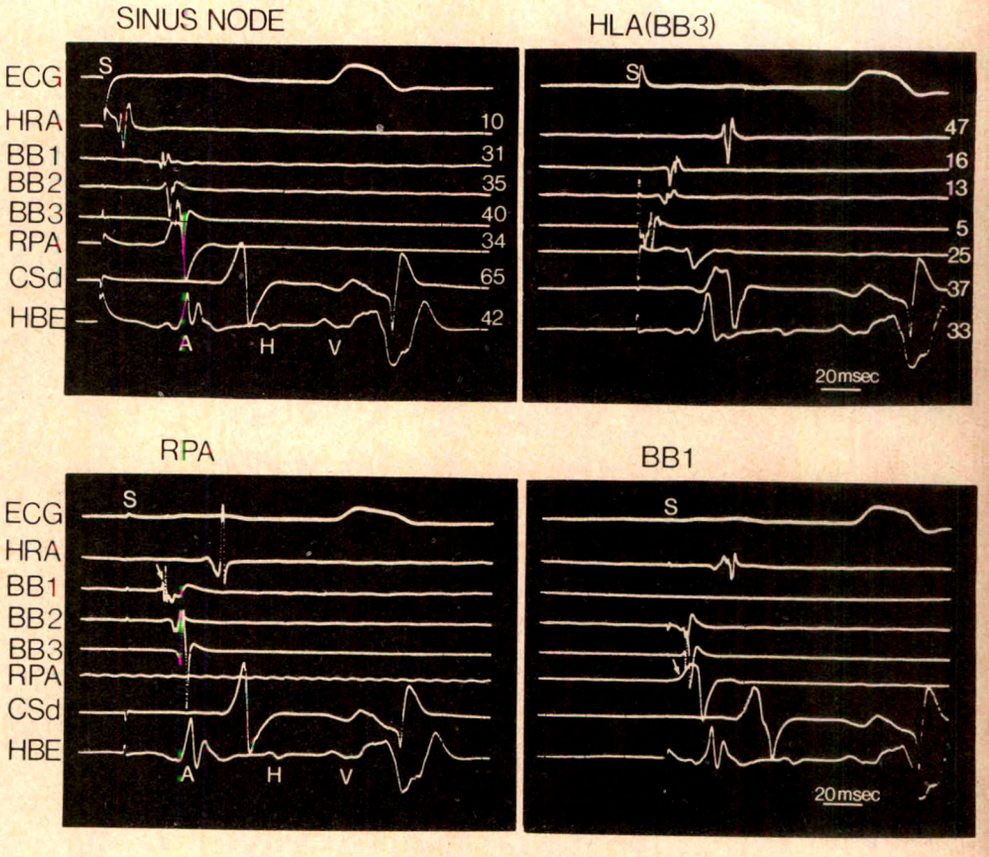


FIGURE 5. Validation of the right pulmonary arterial electrogram. **Top,** tracings recorded during sinus nodal pacing (**left**) and high left atrial pacing (BB3) (**right**) at a sweep speed of 500 mm/sec. The numbers shown at the **right** of each tracing indicate the intervals (msec) from the stimulus artifact (S) to each electrogram. Note that the onset of the right pulmonary arterial electrogram (RPA) was inscribed after the peak of the BB1 electrogram by 3 msec during sinus nodal pacing (34 versus 31 msec), and by 9 msec during high left atrial pacing (25 versus 16 msec). **Bottom,** tracings recorded during right pulmonary arterial (RPA) pacing (**left**) and Bachmann's bundle (BB1) pacing (**right**) at a sweep speed of 500 mm/sec. Right pulmonary arterial pacing produced the earliest atrial activation in the BB1 electrode (**small arrow, lower left panel**), and BB1 pacing produced the earliest activation in the right pulmonary artery. Note the similar atrial activation sequence in both panels. The right pulmonary arterial electrogram in the **left panel** and the Bachmann's bundle (BB1) electrogram in the right panel were disconnected for the purpose of pacing. ECG = lead II electrocardiogram; other abbreviations as in Figure 4.

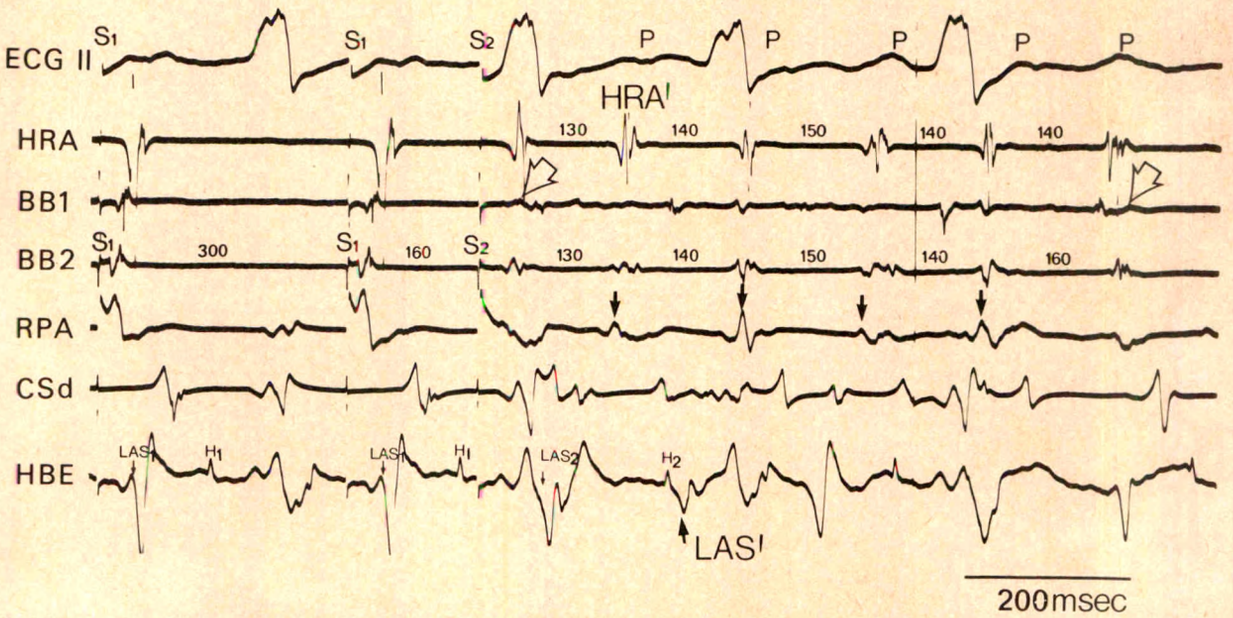


FIGURE 6. An example of Bachmann's bundle reentry tachycardia. The high left atrium was driven at an S_1-S_1 interval of 300 msec, and a premature stimulus (S_2) was introduced 160 msec after the eighth S_1. Note the fragmentation of the Bachmann's bundle (BB2 and BB1) electrograms after S_2 (**first white arrow**), producing supraventricular tachycardia associated with continuous asynchronous low amplitude deflections in the BB1 electrogram (**between two white arrows**). During this Bachmann's bundle reentry tachycardia, the onset of the right pulmonary arterial (RPA) electrogram (**black arrows**) clearly preceded the high right atrial, distal coronary sinus and low atrial septal (in the His bundle electrogram [HBE]) activations. Note the "high to low" right atrial activation sequence during this reentry tachycardia (the high right atrial electrogram of the first reentry beat, HRA′, preceded the low atrial septal electrogram in the His bundle electrogram, LAS′). ECG II = lead II of the surface electrocardiogram; other abbreviations as in Figure 4.

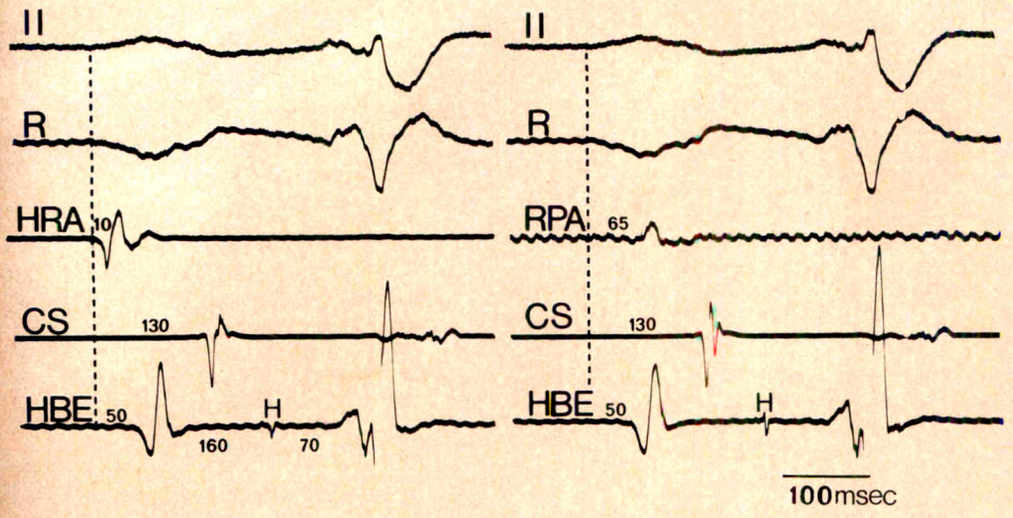


FIGURE 7. Case 1. Three atrial electrograms obtained by the catheters indicated in Figure 2, and simultaneously recorded leads II (II) and aVR (R) from a patient with right bundle branch block and left axis deviation (**left**). Activation of the high right atrium (HRA), low left atrium (in the distal coronary sinus [CS] catheter) and low atrial septum (in the His bundle electrogram [HBE]) occurred 10, 130 and 50 msec, respectively, after the onset of the P wave in leads II and aVR. The high right atrial catheter was advanced into the right pulmonary artery (RPA) to record Bachmann's bundle electrogram (**right**). The right pulmonary arterial electrogram was inscribed 65 msec after the onset of the P wave.

These observations suggest that the right pulmonary arterial electrode was indeed in close proximity to Bachmann's bundle and could register the timing of Bachmann's bundle activation.

Activation sequence during Bachmann's bundle reentry: The right atrial activation sequence of the reentry beats originating in the region of Bachmann's bundle was not specific for the identification of these arrhythmias. Inconsistent patterns of "high to low" (three dogs), "low to high" (seven dogs) or simultaneous "high and low" (two dogs) right atrial activation sequences were observed during Bachmann's bundle reentry. However, in all instances, the right pulmonary arterial electrode was able to register the earliest atrial activation corresponding to Bachmann's bundle activation. Thus, the right pulmonary arterial electrogram preceded activation of the high right atrium, low atrial septum and low left atrium. Figure 6 illustrates a representative example of Bachmann's bundle reentry tachycardia. A premature stimulus (S_2) introduced in the high left atrium (S_1–S_2 interval = 160 msec) significantly increased the fragmentation of Bachmann's bundle electrograms (BB1 and BB2), resulting in supraventricular tachycardia at a cycle length of 130 to 160 msec. During this Bachmann's bundle tachycardia, the right pulmonary arterial electrogram clearly preceded the high right atrial (HRA), low left atrial (CSd) and low atrial septal (HBE) electrograms (indicated by black vertical arrows). A diagnosis of sinus nodal reentry tachycardia could have been made in this tracing if only the conventional atrial electrograms (the high right atrium and His bundle) were utilized. Note that the high right atrial electrogram (HRA′) was inscribed before the low atrial septal electrogram (LAS′) during this tachycardia.

Right Pulmonary Arterial Electrograms in Human Studies

Case 1. The patient was a 54 year old woman with a history of paroxysmal supraventricular tachycardia. The electrocardiogram showed first degree A-V block (P-Q = 0.28 second) and complete right bundle branch block with left axis deviation. In Figure 7, left panel, standard electrocardiograms (leads II and aVR), the high right atrial electrogram, the distal coronary sinus electrogram and the His bundle electrogram are shown. In the right panel, the high right atrial electrode was advanced into the right pulmonary artery. The right pulmonary arterial electrogram was inscribed 55 msec after the high right atrial electrogram, 15 msec after the low atrial septal electrogram and 65 msec before the distal coronary sinus electrogram.

Case 2. The patient was a 50 year old woman with recurrent precordial chest distress and palpitations. The surface electrocardiogram, lead Y (Fig. 8), showed repetitive runs of supraventricular tachycardia with negative P waves. Figure 9, top panel, shows a lead V_1 electrocardiogram, high right atrial electrogram and His bundle electrogram. The high right atrial catheter was advanced into the proximal right pulmonary artery (RPA, BB) (Fig. 9, bottom panel). These two tracings were consecutively recorded. In both the upper and lower

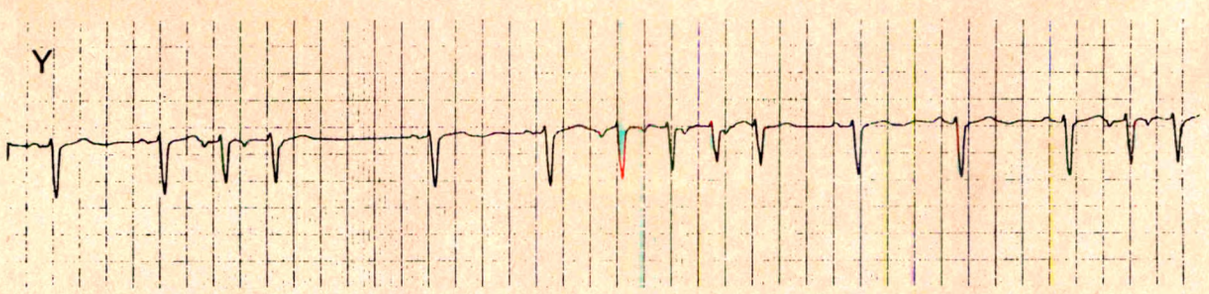


FIGURE 8. Case 2. A surface electrocardiogram (lead Y) showing runs of supraventricular tachycardia.

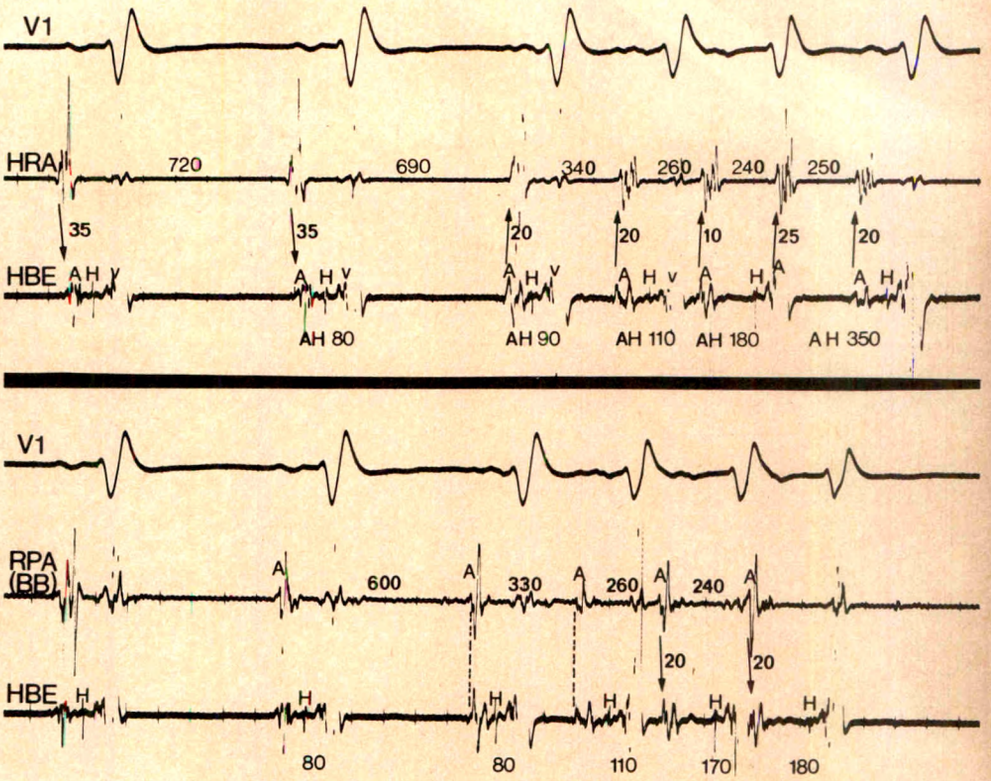


FIGURE 9. Case 2. Atrial electrograms and lead V_1 electrocardiogram recorded at a paper speed of 100 mm/sec. In the **top panel,** the high right atrial electrogram (HRA) was recorded along with the His bundle electrogram (HBE). In the **bottom panel,** the high right atrial catheter was advanced into the proximal right pulmonary artery (RPA). In both panels, the first two beats represent spontaneous sinus beats, and the third beat is an atrial premature beat initiating a short run of supraventricular tachycardia. Note that during this tachycardia the right atrial sequence was "low to high" (**top panel**), but the right pulmonary arterial electrogram was inscribed simultaneously (**dotted lines**) with or before (**arrows**) the low atrial septal activation in the His bundle electrogram (**bottom panel**). All numbers are expressed in msec; time lines are 100 msec apart. v = ventricular electrogram; V1 = lead V_1 of the surface electrocardiogram; other abbreviations as in Figure 4.

panels, the first two complexes represent a spontaneous sinus rhythm. The premature complex (third beat) induced short runs of supraventricular tachycardia. During sinus rhythm, the high right atrial electrogram was inscribed 35 msec before low atrial septal activation as recorded in the His bundle electrogram (first two beats in the top panel). The atrial electrogram recorded from the right pulmonary artery was inscribed simultaneously with the low atrial septal electrogram during sinus rhythm (in the first two beats, bottom panel). The right atrial activation sequence of the premature atrial beat and the following supraventricular tachycardia was "low to high" (the low atrial septal electrogram preceded the high right atrium by 10 to 25 msec) in the top panel. Therefore, the diagnosis of A-V nodal reentry or reentry within the low right atrium could have been made. However, the right pulmonary arterial electrogram recorded during tachycardia was inscribed simultaneously (first two beats) and clearly preceded the low atrial septal electrogram in the last two beats. Hence, the site of impulse formation during this tachycardia could have been located within or close to the high left atrium or near the region of Bachmann's bundle.

Discussion

Bachmann's bundle reentry and supraventricular tachycardia: Longitudinal dissociation within Bachmann's bundle has been identified as a mechanism of supraventricular tachycardia.[9] This phenomenon is characterized by fragmentation of Bachmann's bundle electrograms and is associated with concomitant reentry within this region. Bachmann's bundle reentry may mimic sinus or A-V nodal reentry if the P wave configuration and right atrial activation sequence of "high to low" or "low to high" are the only criteria considered[9] (Fig. 6). Therefore, the exact mechanism of this arrhythmia could never be identified unless electrograms were obtained from the region of Bachmann's bundle. Furthermore, the significance of Bachmann's bundle electrograms was emphasized by Waldo et al.[7,8] in studying atrial activation sequence in relation to P wave polarity in lead II in canine and human hearts. The relative timing of impulse arrival at Bachmann's bundle as compared with the low left atrium, and the direction of impulse spread into and from Bachmann's bundle, were shown to play crucial roles in determining P wave polarity. Hence, recording of Bachmann's bundle activation is necessary in localizing the precise site of reentry during supraventricular tachycardia.

Reliability of right pulmonary arterial catheter in recording Bachmann's bundle electrogram: The results of our study demonstrate that despite the indirect contact of the right pulmonary arterial electrode with the atrial tissues, this catheter was able to record atrial electrograms from the region of Bachmann's bundle in all canine experiments. These electrograms were validated by simultaneously recorded Bachmann's bundle electrograms with plunge wire electrodes during pacing of the sinus node, high left atrium and right ventricle in each dog. The right pulmonary arterial electrogram could approximate the timing of atrial activation in the region of Bachmann's bundle within 5 to 10 msec during anterograde as well as retrograde atrial activation. This technique was further verified by right pulmonary arterial stimulation and direct Bachmann's bundle stimulation (Fig. 5). Pacing from the right pul-

monary artery produced the earliest atrial activation in Bachmann's bundle, and vice versa.

Reliability of the right pulmonary arterial electrode in distinguishing Bachmann's bundle reentry from other types of atrial or A-V nodal reentry was also confirmed (Fig. 6). The right pulmonary arterial electrogram was consistently inscribed before the high right atrial, low atrial septal and low left atrial electrograms during Bachmann's bundle reentry regardless of the right atrial activation sequence.

Clinical implications: The proximal portion of the human right pulmonary artery is anatomically in close proximity to the superior wall of the left atrium[12] and thus to Bachmann's bundle. Although validation of the right pulmonary arterial catheter technique in the human heart is yet to be established, preliminary observations in the four patients reported indicate that good quality atrial electrograms can be recorded from the proximal right pulmonary artery. From the temporal relation of this electrogram to the other atrial electrograms (Fig. 7 and 9), similar to that observed in the canine experiments, it appears that the human right pulmonary arterial electrogram could also reflect atrial activation from the region of Bachmann's bundle.

Distal coronary sinus catheter electrode techniques[13] and filtered esophageal electrocardiography[14] have been utilized to record posteroinferior left atrial activity. More recently, Amat-y-Leon et al.[15] have used the main pulmonary artery to record atrial activation from the left atrial appendage that was inscribed at the end of the P wave. Recording an additional electrogram from the region of Bachmann's bundle with a right pulmonary arterial catheter could provide certain advantages to more precisely evaluate the mechanisms of supraventricular tachycardias. As shown in Figure 9, the diagnosis of retrograde atrial activation from the low right atrium or the A-V nodal tissues should not be made only on the basis of P wave configuration or right atrial activation sequence, alone or in combination, because early activation in the high left atrium or Bachmann's bundle could be associated with the "low to high" right atrial activation sequence[9,16] (Fig. 5A, right panel). Inscription of the right pulmonary arterial electrogram before low atrial septal activation excluded the possibility of A-V nodal reentry (Fig. 9).

This technique could also provide a more precise method for evaluating interatrial conduction. Several previous clinical studies[17–19] have measured the interval from the high right atrial activation to the low left atrial activation, recorded in the distal coronary sinus electrogram or esophageal electrogram as interatrial conduction time. However, the right pulmonary arterial electrogram could possibly separate interatrial conduction time from left intraatrial conduction time.

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Natural History of Wolff-Parkinson-White Syndrome Discovered in Infancy

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The prognosis of 20 infants with a diagnosis of Wolff-Parkinson-White syndrome under 1 year of age is presented. Children were followed up from 1 to 19 years (mean 9 years). Seven patients had associated congenital heart disease. Analysis of the associated arrhythmias revealed episodes of supraventricular tachycardia in 18 (90 percent). During paroxysmal supraventricular tachycardia the QRS complex was normal in seven and wide in nine children. Categorizing patients into groups according to the width of the QRS complex and the presence or absence of a delta wave during tachycardia helps in understanding and planning therapy. Eighteen patients had a stable or improved course with growth but two patients with tetralogy of Fallot died postoperatively with resistant supraventricular tachycardia. The high prevalence rate of supraventricular tachycardia during infancy which later decreases or disappears could be explained by the different electrophysiologic responses between normal and accessory pathways during the fast heart rate characteristic of this young age.

Invasive electrophysiologic studies are indicated in children older than 1 year of age who remain symptomatic and in all children being considered for cardiac surgery regardless of the effectiveness of the preoperative therapy.

The electrophysiology of the Wolff-Parkinson-White syndrome has been defined in recent studies with bundle of His recordings, intracardiac stimulation and epicardial excitation mapping. In selected cases, the successful surgical management of this condition has demonstrated the accuracy and reliability of these techniques.[1] However, the indications for invasive electrophysiologic studies in infants and children need further analysis. This report provides information on the long-term prognosis of infants with Wolff-Parkinson-White syndrome and considers the indications for electrophysiologic studies.

Material and Methods

Twenty infants with Wolff-Parkinson-White syndrome were admitted to the Medical College of Virginia Hospital or Clinics from 1957 to 1976. The atrioventricular (A-V) form[2] of Wolff-Parkinson-White syndrome was recognized in each patient before the 1st birthday. Patients with other forms of preexcitation were not included in this study. The diagnosis of Wolff-Parkinson-White syndrome was established on the basis of the accepted electrocardiographic criteria of a short P-R interval and wide QRS duration with a delta wave producing early slurring. Standard criteria were used to further classify the abnormality as type A, B or C.[3–5]

Clinical evaluations, performed at least annually, consisted of a medical history, including detailed description of the frequency, duration and symptoms of tachycardia, physical examination, chest roentgenogram, electrocardiogram and Frank vectorcardiogram. A record of all medications administered was recorded at each evaluation. Patients with associated structural congenital heart defects had cardiac catheterization and angiography.

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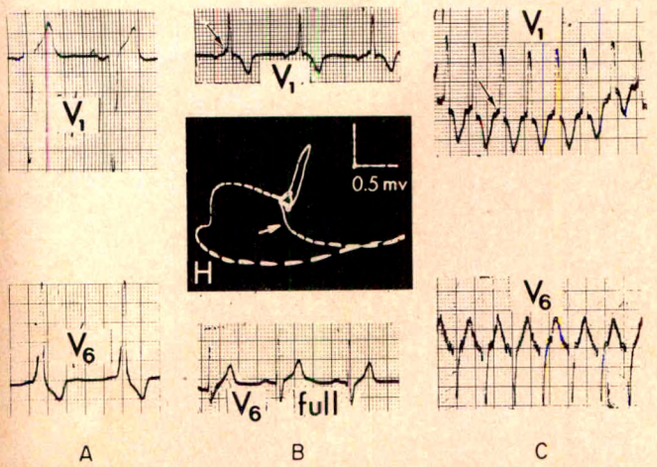


FIGURE 1. Case 10. Coarctation of aorta and mitral valve disease. **A,** current electrocardiogram showing Wolff-Parkinson-White pattern, type B. **B,** electrocardiogram and Frank vectorcardiogram in infancy showing type A pattern. **Arrows** denote delta waves. **C,** electrocardiogram during supraventricular tachycardia. Note the wide QRS complex (0.08 second at a heart rate of 214 beats/min) and delta wave **(arrow).** H = horizontal plane.

At the last examination, the 20 patients, 14 male and 6 female, ranged in age from 1 to 19 years (mean 9 years). A positive family history for tachyarrhythmia was found in only one patient. Type A Wolff-Parkinson-White was observed in 10 patients, type B in 8, both types A and B in 1 (Fig. 1) and type C in one (Table I). Seven patients had associated congenital heart defects (Table I).

Results

Supraventricular tachycardia: This arrhythmia occurred in 18 patients. It was documented by electrocardiographic recordings in 16 and by an unequivocal history of tachycardia with sudden onset and termination in 2. During supraventricular tachycardia, the QRS configuration and duration was normal in seven patients (Group A); in nine others the QRS contour was wide and bizarre (Group B). In these nine patients the mechanism of tachycardia can be differentiated according to the presence or absence of a delta wave. In seven patients (Group B-1), paroxysmal supraventricular tachycardia occurred with a delta wave present. This finding suggests that anterograde conduction occurred through an accessory pathway and retrograde conduction through either the normal pathway or a second accessory pathway (Fig. 2). In two patients (Group B-2), paroxysmal supraventricular tachycardia occurred with no delta wave. This finding suggested that anterograde conduction occurred through the normal pathway with aberrancy and retrograde conduction through an accessory pathway (Fig. 3).

During infancy the patients were separated into four groups according to the disability from tachycardia:

Group I (three infants): Two had no tachyarrhythmia and one had only rare tachyarrhythmia lasting less than 5 minutes; they remained asymptomatic as infants without medical therapy.

Group II (two infants): Both had brief tachyarrhythmia and were treated as outpatients.

Group III (two infants): Both were hospitalized with tachycardia but had no signs or symptoms of congestive heart failure.

Group IV (13 infants): These patients were hospitalized with tachyarrhythmia that produced congestive heart failure. Seven of these patients are now receiving prophylactic medication. Only two have experienced episodes of tachyarrhythmia lasting more than 3 hours (Fig. 4).

TABLE I

Clinical Data in 20 Cases of Wolff-Parkinson-White Syndrome

Case no.	Sex	WPW Type	Congential Heart Disease	Age at Diagnosis	Follow-Up Period (yr)
1	M	A	...	1 day	2
2	M	B	...	10 days	16
3	M	A	...	3 mo	12
4	M	A	...	6 wk	6
5	M	A	...	9 days	6
6	M	A	Tetralogy of Fallot	2 days	6
7	M	A	...	20 days	19
8	M	A	...	6 wk	10
9	F	A	...	12 hr	5
10	M	A + B	Coarctation of aorta; mitral valve disease	10 mo	14
11	F	B	...	9 mo	16
12	F	B	Ebstein's anomaly	1 day	2
13	M	B	...	1 day	1
14	M	B	Ebstein's anomaly	2 days	11
15	F	B	Ebstein's anomaly	1 wk	9
16	M	A	Tetralogy of Fallot	3 mo	5
17	M	C	...	3 mo	15
18	F	B	...	4 mo	15
19	F	A	Cardiomyopathy	10 mo	9
20	M	B	...	1 mo	2

WPW = Wolff-Parkinson-White syndrome.

Treatment of supraventricular tachycardia: Various treatments were used for conversion of supraventricular tachycardia to normal sinus rhythm (Table II). Digitalis alone was effective in 10 patients; in 7 others additional drugs were needed for conversion. Five patients required more than two medications. Only one patient responded to vagal maneuvers. In four patients supraventricular tachycardia persisted for more than 24 hours before and after admission for the first recognized episode.

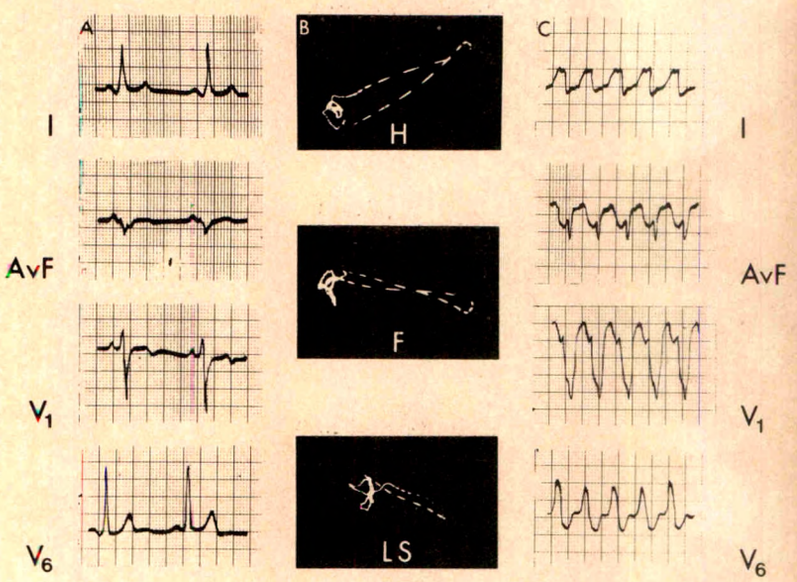


FIGURE 2. Case 14. Patient with Ebstein's anomaly. **A,** sinus rhythm with Wolff-Parkinson-White pattern, type B. **B,** Frank vectorcardiogram showing Wolff-Parkinson-White pattern, type B. **C,** during supraventricular tachycardia. A wide QRS complex and delta wave are present. F, H and LS indicate frontal, horizontal and left sagittal plane, respectively.

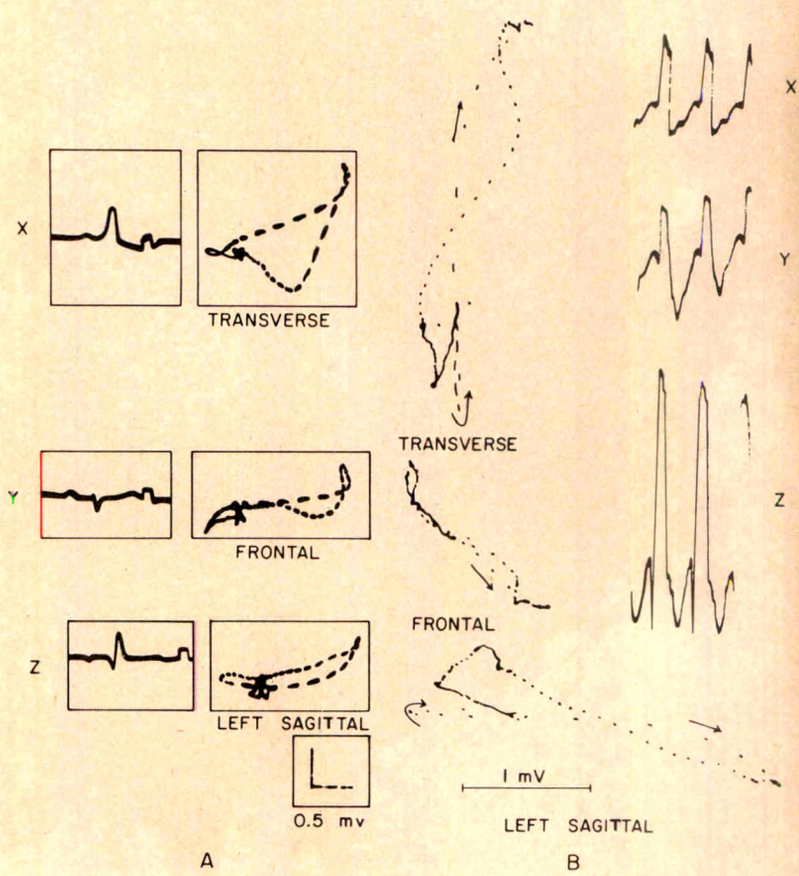


FIGURE 3. Case 15. Frank vectorcardiogram during sinus rhythm and supraventricular tachycardia in patient with Ebstein's anomaly. **A,** initial QRS delay during sinus rhythm. **B,** Mid temporal delay during supraventricular tachycardia with a wide QRS complex.

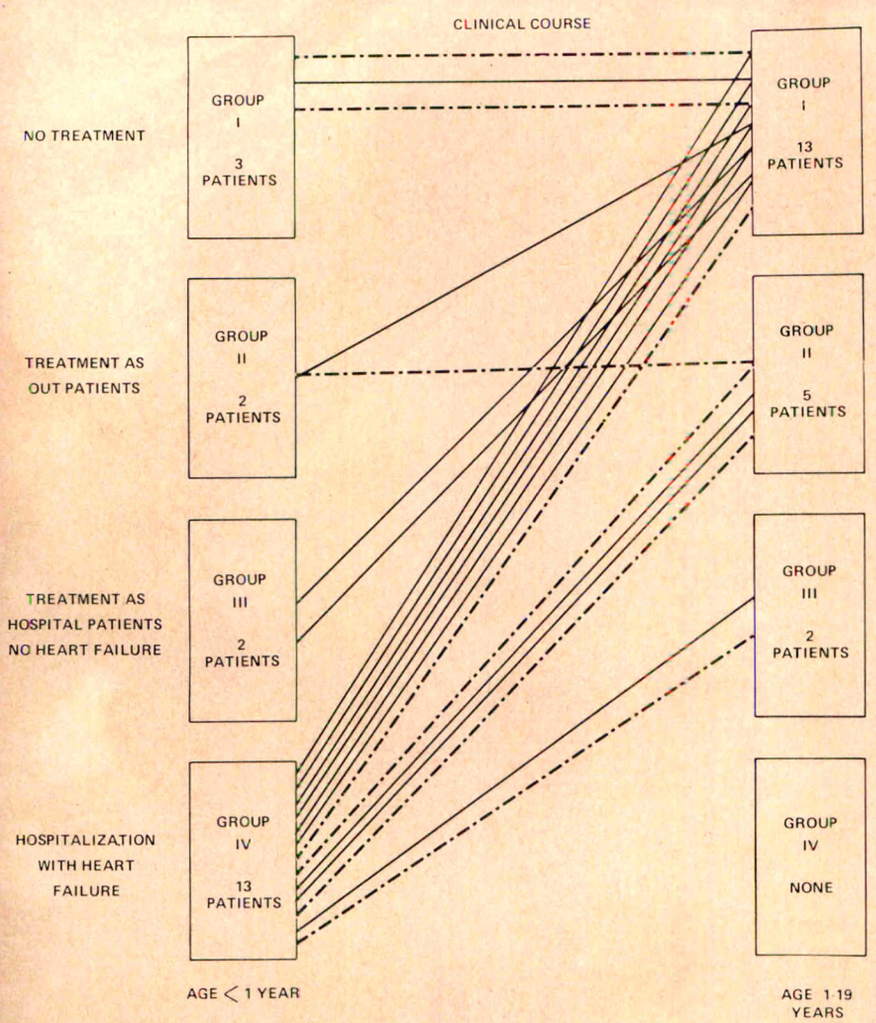


FIGURE 4. Diagram showing clinical course in 20 cases. The **dotted line** indicates associated congenital heart disease.

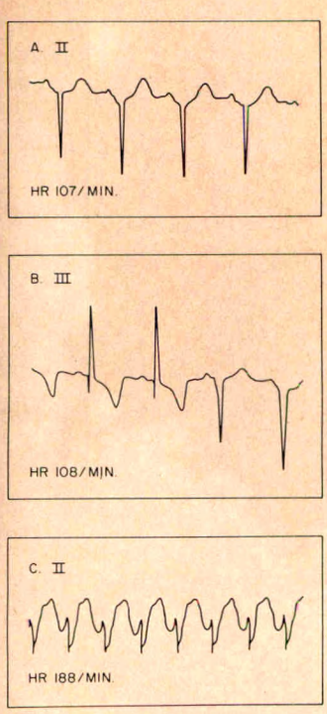


FIGURE 5. Case 16. Preoperative and postoperative electrocardiograms in a patient with tetralogy of Fallot. **A,** lead II 2 years before operation showing normal conduction. **B,** lead III 2 years before operation showing intermittent Wolff-Parkinson-White conduction. **C,** lead II immediately after intracardiac operation showing supraventricular tachycardia and wide QRS complexes, probably due to right bundle branch block. HR = heart rate.

Electrical cardioversion was used in five patients. It was successful in three, two with resistant tachyarrhythmia and one with severe heart failure. In two children with tetralogy of Fallot, electrical cardioversion failed to convert a lethal postoperative arrhythmia.

Several drugs were used to prevent supraventricular tachycardia (Table II). Digitalis alone was effective in five patients and propanolol provided control in an additional five. The arrhythmia was controlled by Dilantin in two patients and by quinidine in two others. In the remaining four patients, combinations of three or more drugs were necessary for prevention. While receiving prophylactic therapy to prevent recurrence of tachyarrhythmia, only two patients experienced episodes of rapid heart action lasting more than 3 hours. There was no significant difference in the success of prevention related to narrow or wide QRS complexes during tachyarrhythmia.

Discussion

Prevalence: The prevalence rate of Wolff-Parkinson-White pattern for infants and children in a random population is between 0.4 and 1.0 per 1,000. In children referred for cardiac evaluation the rate is 5.0 per

TABLE II

Summary of Therapy in 18 Cases*

Case no.	Conversion: Vagal Maneuvers	Digitalis	Propranolol	Quinidine	Reserpine	Prostigmine	Dilantin	Lidocaine	DC Cardioversion	Prevention: Digitalis	Propranolol	Quinidine	Reserpine	Dilantin
Normal QRS During SVT (Group A)														
1	...	+	...	...	...	...	...	...	...	+	...	...	...	...
2	...	+	...	...	...	...	...	...	...	+	+	+	+	...
3	...	+	...	...	+	+	...	...	+	+	+	+	+	+
4	...	+	...	...	...	...	...	...	+	+	+	...	...	...
5	...	+	...	...	...	...	...	...	...	+	...	...	...	...
6	...	+	...	...	...	...	+	...	+	+	...	...	...	+
7	...	+	...	...	...	+	...	...	...	+	...	...	...	...
Wide QRS With Delta Waves During SVT (Group B-1)														
8	+	...	...	...	...	...	...	...	...	+	...	...	...	...
9	...	+	...	...	...	...	...	...	...	+	+	...	...	...
10	...	+	...	...	...	...	...	...	...	+	+	...	...	...
11	...	+	...	...	...	...	...	...	...	+	...	+	...	...
12	...	+	...	+	+	...	+	...	...	+	+	+	+	...
13	...	+	...	...	...	...	...	...	...	+	+	...	...	...
14	...	+	...	...	...	...	...	...	...	+	...	...	...	+
Wide QRS Without Delta Waves (Group B-2)														
15	...	+	...	...	+	+	+	...	+	+	+	+	+	+
16	...	+	...	...	...	...	+	+	+	...	+	...	...	...
SVT on History Only														
17	...	+	...	...	...	...	...	...	...	+	...	...	...	...
18	...	+	...	...	...	...	...	...	...	+	...	+	...	...

* Two patients (Cases 19 and 20) had no supraventricular tachycardia and received no antiarrhythmic therapy.
SVT = supraventricular tachycardia.

1,000.[6–8] Paroxysmal supraventricular tachycardia, present in 40 to 80 percent,[6–9] is usually infrequent, brief and not associated with symptoms. However, in a small number of patients disabling and even fatal tachycardia can occur as the result of fast ventricular response, long duration or associated myocardial dysfunction.[9,10]

The prevalence rate of supraventricular tachycardia in our patients during infancy (90 percent) was higher than the rate in the general population. This probably reflects the earlier patient referral for underlying congenital heart disease or cardiac failure from tachycardia.

Family history: A familial prevalence of Wolff-Parkinson-White has been reported.[11–15] In the families of our patients electrocardiograms were not recorded and, therefore, the familial prevalence of conduction anomaly is not known. A history of supraventricular tachycardia was present in only one family. In this family the patient's mother and maternal grandmother required drugs to control recurrent tachycardia. They had normal electrocardiograms during normal sinus rhythm with no Wolff-Parkinson-White pattern.

Congenital heart defects: Associated cardiac defects were present in one third of the 20 patients. This prevalence is similar to that previously reported in children[10] and in adults.[1] The high prevalence rate of Ebstein's anomaly in our patients (45 percent) is also noted in earlier reports.[1,8] All of our patients with Ebstein's anomaly had the characteristic type B preexcitation form.

The two patients who died at the time of surgical correction of tetralogy of Fallot are of special interest. Both had type A Wolff-Parkinson-White pattern. Before operation one responded well to the preventive therapy and the other never had attacks of paroxysmal tachycardia or other arrhythmias. During technically uncomplicated surgical correction supraventricular tachycardia (Fig. 5, rate 187/min) developed that did not respond either to drug treatment or to electrical conversion. The arrhythmia significantly contributed to the death of each patient.

Electrophysiology: In patients with Wolff-Parkinson-White conduction abnormality, supraventricular tachycardia is the most common arrhythmia. It occurred in 90 percent of our patients. In the infant group the prevalence rate (56 percent) of supraventricular tachycardia with a wide QRS complex was higher than that reported by others. Among 35 children with Wolff-Parkinson-White syndrome, Giardina et al.[10] found 4 with a wide QRS complex during supraventricular tachycardia. During tachycardia the configuration of the QRS complex is important in determining treatment because different mechanisms respond to different medications.

It has been demonstrated with the single test stimulus method that an increase in the prematurity of the test pulse results in an increase in the area of the ventricle activated by the bypass. This is the result of increasing the A-V nodal transmission time with increasing prematurity at a given atrial premature beat. In contrast

to the A-V node, where the effective refractory period lengthens with increasing heart rates, the effective refractory period of the bypass shortens with increased heart rates.[16] This different response to tachycardia between normal and accessory pathways results in an expansion of the echo zone that facilitates the initiation of supraventricular tachycardia. Furthermore, premature beats are not always necessary to initiate tachycardia.[17] In infants, the cycle length is normally short at rest and is even shorter with excitement, fever or crying. Therefore, in babies with Wolff-Parkinson-White syndrome the echo zone is widely open, and attacks of circus movement tachycardia are prone to occur during this period of time. This hypothesis is supported by the high prevalence rate of reentry tachycardia utilizing the accessory pathway for anterograde conduction.

Clinical course: The quality and length of life for children with Wolff-Parkinson-White pattern without cardiac dysrhythmia is normal.[9] The mild dyskinetic ventricular contractions that accompany this conduction abnormality[18–20] are tolerated without difficulty. In adult patients with associated arrhythmias, a higher mortality rate was reported, especially among young adults. The majority of these patients had associated heart disease.[21] In children, sudden death has been reported even in the absence of associated heart disease.[22] The morbidity and mortality of Wolff-Parkinson-White syndrome are significantly less in infants and children without structural defects. Of the 13 patients with significant symptoms during infancy or early childhood (Group IV), only 6 required prophylactic drug therapy at their last evaluation and only 2 had experienced episodes of tachyarrhythmia lasting more than 3 hours. Moreover, of the three Group I patients who were asymptomatic as infants, each is now asymptomatic. All previous reports indicate that the condition of infants with frequent supraventricular tachycardia improves dramatically during the 1st year of life. Unlike the condition of adults, that of infants rarely deteriorates with time. The cause for this apparent age difference is not understood. One explanation for the benign course in children has been offered by James[23] who hypothesized that a transient Wolff-Parkinson-White pattern in infancy may indicate postnatal resorption of aberrant septal A-V connections. In our group of patients, although the episodes of supraventricular tachycardia decreased, the Wolff-Parkinson-White pattern persisted in 90 percent of the patients.

Therapy: During supraventricular tachycardia two distinct patterns of QRS complexes are found in patients with the Wolff-Parkinson-White syndrome: normal QRS (Group A) and wide QRS (Group B). Patients in Group B can be further separated into subgroups B-1, if a delta wave is present, and B-2, if a delta wave is absent but there is aberrancy.

In patients in Group A, drugs for converting paroxysmal supraventricular tachycardia should increase the effective refractory period of the normal pathway. Both digitalis and propranolol have this action and have been used successfully in many cases (Table II). In Group B, direct current cardioversion is preferable to drugs because it is often difficult to distinguish ventricular from supraventricular tachycardia and to analyze the type of supraventricular tachycardia during the first attack when tracings with sinus rhythm are not available for comparison. Although we have used digitalis in the past in patients in Group B, we believe that cardioversion is preferable when the QRS complex is wide.

To prevent supraventricular tachycardia in Groups A and B-2, we suggest increasing the effective refractory period of the normal pathway and the use of drugs such as digitalis (first choice) and adding propranolol as needed.

In patients with wide QRS tachycardia, the choice of a prophylactic drug is difficult. Wellens and Durrer[24] demonstrated that digitalis decreases the effective refractory period of the anomalous pathway and may accentuate the ventricular response during arrhythmias. Although this risk of digitalis was not confirmed in our experience (Table II), we believe that quinidine may be the drug of choice in patients in Group B-1. This drug increases the effective refractory period of the anomalous pathway and decreases the incidence of premature beats initiating paroxysmal supraventricular tachycardia. The classification of supraventricular tachycardia according to QRS width may provide an indication for a specific drug, as suggested here. However, because of the small number of our patients our study cannot provide a definitive indication of its usefulness in predicting the benefit.

Indications for invasive electrophysiologic studies: Such studies have been reported in very few infants and children with Wolff-Parkinson-White syndrome and were not performed in our patients. A retrospective analysis of the clinical course of these 20 patients suggests that invasive electrophysiologic studies should be considered in: (1) children more than 1 year of age who remain symptomatic (classes III and IV), and (2) in all infants and children for whom cardiac surgery is necessary regardless of the course of the disease or the effectiveness of therapy. Our experience in the two patients operated on showed that this is a high risk group and that programmed electrical stimulation studies should be considered part of their preoperative evaluation. With intracardiac correction, the surgical trauma and the hemodynamic and metabolic changes may alter the preoperative properties of the two pathways, resulting in serious arrhythmias. Consequently, all patients with Wolff-Parkinson-White syndrome should have temporary pacing electrodes implanted at operation. Preoperative planning for overdriving any postoperative arrhythmia is essential.

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Electrophysiologic Studies After Mustard's Operation for d-Transposition of the Great Vessels

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Electrophysiologic studies were performed in 16 patients after Mustard's operation for d-transposition of the great vessels. Standard 12 lead electrocardiograms showed the following rhythms: "sinus" (10 patients), junctional (4 patients), atrial flutter (1 patient) and alternating sinus and junctional (1 patient). Overdrive atrial stimulation was used to determine sinus nodal recovery time in the 16 patients. Atrial and atrioventricular (A-V) nodal effective refractory periods were determined in 12 patients utilizing the atrial extrastimulus technique. Twenty-four hour Holter electrocardiographic monitoring was performed in 15 patients. Ten (63 percent) of the 16 patients had abnormal sinus nodal recovery time. The atrial effective refractory period was prolonged in 4 (33 percent) of the 12 patients in whom it was measured. All 12 patients had a normal A-V nodal effective refractory period. Previously undetected arrhythmias were found in all patients when the 24 hour Holter electrocardiogram was compared with the standard electrocardiogram. Atropine shortened the sinus nodal recovery time, atrial effective refractory period and A-V nodal effective refractory period in all patients studied. One patient, whose junctional pacemaker was first to recover after termination of atrial pacing, had conversion to sinus rhythm and normal sinus nodal recovery time after administration of atropine.

This study indicates (1) that a diseased sinus node and interrupted atrial pathways are involved in the genesis of arrhythmias after Mustard's operation, and (2) that adequate evaluation of arrhythmias in patients after this operation requires not only the standard electrocardiogram, but also a 24 hour Holter monitor, His bundle electrograms and determination of sinus nodal recovery time and atrial and A-V nodal effective refractory periods.

The intraatrial baffle (Mustard's) operation for physiologic correction of transposition of the great vessels represents a major advance in the treatment of this congenital lesion. Although the short-term results have been encouraging, the long-term prognosis remains unknown. Pulmonary venous and venae caval obstructions, tricuspid valve insufficiency and arrhythmia have been reported to occur several years after Mustard's operation.[1–4]

Rhythm disturbances continue to be a major postoperative problem. Several modifications in the baffle operation have been made to avoid injury to the conduction system.[5,6] These have resulted in a significant decrease in postoperative arrhythmias.[7] However, a longer follow-up period will be necessary to determine fully the importance of these modifications.

Although there is an abundance of data concerning the hemodynamic consequences after Mustard's operation, many questions regarding the etiology of postoperative arrhythmias and conduction disturbances are still debated. In this communication we emphasize the electrophysiologic

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findings encountered during postoperative clinical and hemodynamic studies.

Materials and Methods

Case material: Sixteen patients aged 14 months to 9 years were studied 0.5 to 6 years after Mustard's operation. All patients had had previous palliative procedure (balloon atrial septostomy, atrial septectomy, or both). Before operation, all children had sinus rhythm and presented no atrioventricular (A-V) conduction defects. Fourteen of the 16 patients had transposition of the great vessels without associated defects. One patient had an associated sinus venosus atrial septal defect, and one had associated juxtaposition of the atrial appendages.

Surgical procedure: All patients were operated on under cardiopulmonary bypass. Deep hypothermia and circulatory arrest was used in two patients weighing less than 10 kg. The venae caval cannulas were inserted through purse string sutures placed at the cavoatrial junction. A vertical incision, used to open the right atrium, extended from the right atrial appendage to the inferior vena caval cannula. Before insertion of the baffle, the remaining atrial septum was totally excised and the atrial groove was oversewn.[8] The atrial baffle consisted of pericardium in all but two patients in whom a Dacron® patch was used. The baffle suture line consisted of continuous sutures and passed anterior to the superior vena caval orifice. The coronary sinus drainage entered the pulmonary venous atrium in all but one patient in whom the coronary sinus ostium was cut downward into the left atrium and the suture line placed across the floor of the opened coronary sinus behind the A-V node. In two patients, the pulmonary venous atrium was enlarged with a pericardial patch.

Methods: Parents were informed of the nature of the study and informed consent was obtained.

Cardiac catheterization was performed under light sedation (hydroxyzine hydrochloride, 1 mg/kg body weight, and meperidine, 1 mg/kg). No patient was taking cardiac drugs for at least 48 hours before the study. Two electrode catheters were utilized. The first catheter (bipolar) was used for atrial pacing. It was passed through the femoral vein and positioned at the junction of the superior vena cava and systemic venous atrium. The second catheter (tripolar) was passed through the femoral artery and placed in retrograde fashion across the aortic valve to record the His bundle electrogram. The external electrocardiographic lead II was recorded before, during and after the cessation of atrial pacing. Recordings were obtained on a multichannel oscilloscope recorder at a paper speed of 100 mm/sec.

Two modes of pacing were used: (1) pacing with continuously increasing stimulus frequency until Wenckebach type second degree (A-V) block developed or until an atrial rate of 200/min with 1:1 conduction was achieved, and (2) continuous pacing for 2 minutes at a rate of 200/min. The latter mode was used to determine sinus nodal recovery time. In three patients (Cases 1, 3 and 10) sinus nodal recovery time was determined at the highest continuous pacing rate possible before the development of A-V Wenckebach block.

Refractory periods were measured utilizing the atrial extrastimulus technique during sinus rhythm. Pacing was provided by a battery-operated pulse generator. In all patients, the pacing studies were repeated 5 minutes after intravenous administration of 0.5 to 1.0 mg of atropine.

Twenty-four hour Holter electrocardiographic monitoring was performed in all but one patient.

Definitions and measurements: *Basic intervals* (P-R, P-H and H-V) were measured as previously described by Abella et al.[11]

TABLE I

Cardiac Rhythm Manifested in Standard Electrocardiogram in 16 Patients After Mustard's Operation

Rhythm	Patients	
	no.	%
"Sinus"	10	62.6
Junctional	4	25
Atrial flutter	1	6.2
Alternating sinus and junctional	1	6.2
Total	16	100

Sinus nodal recovery time was measured from the last atrial paced beat to the following sinus escape beat. The corrected sinus nodal recovery time was determined by subtracting the average P-P interval from the sinus nodal recovery time.

The atrial effective refractory period was defined as the longest S_1–S_2 interval at which the test premature stimulus (S_2) failed to conduct to the atrium; that is, atrial capture failed to occur.

The A-V nodal effective refractory period was defined as the longest A_1–A_2 interval at which H_2 failed to be elicited; that is, the test premature stimulus failed to conduct to the His bundle. A_1 was a low atrial electrogram induced by S_1. A_2 and H_2 were low atrial and His bundle electrograms induced by S_2.

Results

Postoperative conduction defects or arrhythmias in the standard electrocardiogram (Table I): Before cardiac catheterization, 10 patients had sinus rhythm, 4 had junctional rhythm, one had atrial flutter and one had alternating junctional and sinus rhythm. After administration of atropine, one of the four patients with junctional rhythm had conversion to sinus rhythm. The patient with atrial flutter underwent cardioversion in the catheterization laboratory.

A-V conduction intervals (Table II): Data in the study group were compared with those of normal children as established by Abella et al.[11] The P-R, P-H and H-V intervals were normal in all children with sinus rhythm. The H-V intervals were normal in all patients with junctional rhythm.

Atrial pacing with increasing rates caused prolongation of the P-H interval and no change in H-V interval, until second degree A-V (Wenckebach type) block occurred. Thirteen of the 16 patients had no evidence of A-V block at a pacing rate of 200/min. In three patients Wenckebach block developed proximal to the His bundle at rates of 148, 155 and 171/min, respectively (Cases 1, 3 and 10).

Corrected sinus nodal recovery time: Data for the study group were compared with normal values established by El-Said et al.[12] The sinus pacemaker was the first to recover in nine patients. All but two patients (Cases 1 and 13) had evidence of "sinus" rhythm in the standard electrocardiogram. Six of these nine patients had a normal corrected sinus nodal recovery time. A prolonged corrected sinus nodal recovery time was evident in the remaining three patients.

Junctional escape beats before sinoatrial (S-A) nodal recovery were observed in seven patients. Three of these

TABLE II

Summary of Electrophysiologic Data in 16 Children After Mustard's Operation

Case no.	Rhythm: At Rest	Rhythm: After Atropine	Intervals in His Bundle Electrogram (msec): H-R	P-R	P-H	H-V	Atrial Response (rate)		CSNRT: At Rest (msec)	CSNRT: After Atropine (msec)	Comment
1	S,J	S	80	130	95	35	W	155	200	70	. . .
2	S	S	112	120	80	40	(1:1)	200	JER for 22.2 sec	JER	. . .
3	S	S	89	140	110	30	W	171	200	150	. . .
4	S	S	100	130	90	40	(1:1)	200	100	80	. . .
5	AF	S	120	150	115	35	(1:1)	200	JER for 8.2 sec	JER	Cardio-version
6	S	S	90	120	85	35	(1:1)	200	100	70	. . .
7	S	S	95	150	110	40	(1:1)	200	JER for 8.1 sec	JER	. . .
8	S	ND	120	140	105	35	(1:1)	200	80	80	. . .
9	S	ND	98	140	100	40	(1:1)	200	JER for 6.4 sec	—	SVT developed after pacing
10	J	J	75	—	—	40	W	148	JER	JER	. . .
11	J	J	108	—	—	35	(1:1)	200	JER	JER	AF developed
12	S	ND	120	120	90	30	(1:1)	200	280*	ND	Technical difficulty
13	J	S	100	—	—	30	(1:1)	200	460*	130	. . .
14	S	S	95	130	90	40	(1:1)	200	100	80	. . .
15	J	S	80	—	—	40	(1:1)	200	JER for 1.1 sec	140	. . .
16	S	S	90	140	100	40	(1:1)	200	270*	180	. . .

* Abnormal values.
AF = atrial flutter; CSNRT = corrected sinus nodal recovery time; J = junctional rhythm; JER = junctional escape rhythm; ND = study not done; S = sinus rhythm; SVT = supraventricular tachycardia; W = Wenckebach; — = not recorded; . . . = no comment.

patients (Cases 2, 7 and 9) had sinus rhythm, one (Case 5) had atrial flutter and three (Cases 10, 11 and 15) had junctional rhythm as assessed with the random standard electrocardiogram. Therefore, corrected sinus nodal recovery time was not calculated because the junctional tissue, not sinus nodal tissue, was the first to recover after termination of atrial pacing.

Refractory periods of the atrium and A-V node (Table III): Data from the study group were compared with normal data established by DuBrow et al.[13]

Atrial effective refractory period: Data were available for 12 patients. In four patients, the refractory periods could not be determined. In two of these patients (Cases 9 and 11) supraventricular tachycardia developed during atrial pacing, whereas in the other two (Cases 6 and 12) technical difficulties prohibited completion of the study. Four (33 percent) of the 12 patients studied had a prolonged atrial effective refractory period. Corrected sinus nodal recovery time was normal in two of these four patients (Cases 1 and 3) and ab-

TABLE III

Refractory Periods (msec) in 16 Children After Mustard's Operation

Case no.	CL	Before Atropine: AERP	Before Atropine: AVNERP	After Atropine: AERP	After Atropine: AVNERP
1	360	280*	380	240	240
2	350	190	300	180	210
3	290	300*	250	280*	240
4	320	NM	150	NM	120
5	780	180	240	150	120
6	ND	ND	ND	ND	ND: Technical difficulty
7	290	260*	250	230	170
8	ND	ND	ND	ND	ND
9	NM	NM	NM	NM	NM: SVT developed
10	780	230	260	220	250
11	NM	NM	NM	NM	NM: Atrial flutter during paired pacing
12	ND	ND	ND	ND	ND: Technical difficulty
13	310	160	260	150	180
14	280	150	160	80	150
15	380	295*	290	230	205
16	340	235	260	160	160

* Abnormal values.
AERP = atrial effective refractory period; AVNERP = atrioventricular nodal effective refractory period; CL = cycle length; ND = study not done; NM = not measurable; SVT = supraventricular tachycardia.

normal (junctional pacemaker recovery) in the other two patients (Cases 7 and 15).

A-V nodal effective refractory period: This period was normal in all patients studied. The atrial effective refractory period exceeded the A-V nodal effective refractory period in three patients (Cases 3, 7 and 15).

Effect of atropine: Atropine administration decreased the sinus nodal recovery time in all but one patient and normalized the abnormally prolonged corrected sinus nodal recovery time in two patients (Cases 13 and 16). One of the seven patients (Case 15) in whom the junctional pacemaker was first to recover after atrial pacing had conversion to sinus rhythm and normal corrected sinus nodal recovery time after atropine administration. After atropine, the effective atrial and A-V nodal refractory periods shortened in all patients studied.

Twenty-four hour Holter electrocardiographic monitoring (Table IV): Occasional premature atrial contractions and unifocal ventricular premature beats were not considered abnormal. Among 10 patients who manifested sinus rhythm in a random standard electrocardiogram, 4 had episodes of sinus arrest followed by junctional escape rhythm (Cases 2, 3, 9 and 16), 2 had marked bradycardia (Cases 2 and 9), 3 had bursts of paroxysmal atrial tachycardia (Cases 4, 6 and 7) and 4 had multifocal premature ventricular contractions (5 to 8 beats/min) on Holter monitoring.

Two patients who manifested junctional rhythm in the standard electrocardiogram had electrocardiographic evidence of the brady-tachyarrhythmia syndrome (Cases 1 and 15). A short run of ventricular tachycardia was noted in one patient (Case 10). Hence, previously undetected arrhythmias were found in 15 or 100 percent of the patients when the 24 hour Holter electrocardiogram was compared with the standard electrocardiogram.

TABLE IV

Twenty-Four Hour Holter Monitor Findings in 15 Patients After Mustard's Operation

Case no.	Standard ECG	Holter Monitor
1	Sinus and junctional	Intermittent CHB; SB (44/min); bursts of SVT
2	Sinus	SA (1.72 sec) followed by JER; SB (42/min)
3	Sinus	SA followed by JER
4	Sinus	Multifocal PVCs; bursts of SVT
5	Atrial flutter	WAP (after cardioversion)
6	Sinus	WAP with JER; bursts of SVT
7	Sinus	Bursts of SVT
8	Sinus	PVCs (multifocal)
9	Sinus	SB; SA with JER
10	Junctional	SA (2.2 sec) and JER; short run of VT
11	Junctional	PVCs (multifocal)
12	Sinus	Holter monitoring not performed
13	Junctional	SA with JER; 2:1 sinoatrial exit block; SB (41/min)
14	Sinus	PVCs (multifocal)
15	Junctional	Recurrent SA (2.44 sec) resulting in ventricular rate of 27/min followed by JER; bursts of SVT
16	Sinus	Multiform PVCs; SP with JER

CHB = complete heart block; JER = junctional escape rhythm; PVCs = premature ventricular complexes; SA = sinus arrest; SB = sinus bradycardia; SP = sinus pause; SVT = supraventricular tachycardia; WAP = wandering atrial pacemaker.

Discussion

Arrhythmia and conduction disturbances: These are commonly seen after the intraatrial baffle operation for transposition of the great vessels. In their study of 60 postoperative patients, El-Said et al.[3] found only 3 patients who were free of arrhythmia and had sinus rhythm.

The pathogenesis of arrhythmia after Mustard's operation has been a subject of controversy for many years. Gillette et al.[4] concluded that dysfunction of the sinus node was responsible. Internodal conduction intervals, as determined from electrocardiograms recorded from both high and low points in the newly formed systemic venous atrium, were normal in all patients studied. This was taken as evidence against intraatrial block as a mechanism for arrhythmia. Interruption of the internodal pathways was proposed as a possible mechanism for arrhythmia by Isaacson et al.[14] In their series, the sinus node was not directly injured in any of the 32 patients who died from arrhythmia after Mustard's operation or a Blalock-Hanlon or Senning procedure.

Most reports concerning pediatric electrophysiology deal only with the description of conduction intervals. In this investigation we examined the refractory periods in an attempt to elucidate further the etiology of arrhythmias after Mustard's operation and, in particular, the role of intraatrial pathways in the genesis of these rhythm disturbances.

Sinus nodal function: Overdrive atrial stimulation has been shown to be useful in evaluating sinus nodal function in patients with sick sinus syndrome.[15–18] The results of rapid atrial pacing in our study are in agreement with the report of El-Said et al.[12] Ten (63 percent) of our 16 patients had evidence of sinus nodal dysfunction as manifested by prolonged corrected sinus nodal recovery time in 3 patients and by junctional pacemaker recovery in the remaining 7 patients. Post-atrial pacing recovery by a junctional pacemaker instead of sinus nodal pacemaker has been considered an indication of sinus node disease.[4,19] Five of 10 patients with abnormal sinus nodal function manifested normal "sinus" rhythm in the standard 12 lead electrocardiogram. Narula et al.[6] showed that normal sinus rate and rhythm are not an assurance of normal sinus nodal function. Patients with definite sick sinus syndrome may have normal sinus rhythm during the course of their disease.

Determination of sinus nodal function has been advocated as a safe and effective method of identifying patients who are at risk of having prolonged periods of

asystole after spontaneous tachyarrhythmias.[16] This was particularly true in one of our patients (Case 2) who had supraventricular tachycardia during cardiac catheterization followed by 2.3 seconds of asystole. This patient required a cardiac pacemaker 4 months later because of persistent brady-tachyarrhythmia.

Intraatrial conduction: The principal finding of this investigation is the demonstration, using the atrial extrastimulus technique, of previously undocumented prolongation of the atrial effective refractory period in 4 of 12 children after Mustard's operation.

Of these four patients, two had a normal corrected sinus nodal recovery time. One of these two (Case 1) manifested alternating "sinus" and junctional rhythm in a standard electrocardiogram and bursts of supraventricular tachycardia with episodes of complete heart block in a 24-hour ambulatory electrocardiogram. The other patient (Case 3) manifested "sinus" rhythm in the standard electrocardiogram and episodes of sinoatrial block followed by junctional escape rhythm on 24-hour Holter monitoring. The remaining two patients had prolongation of corrected sinus nodal recovery time and the atrial effective refractory period. These findings suggest damage to the sinoatrial node and internodal tracts.

The existence and importance of preferential atrial pathways continue to be debated. MacLean et al.[20] demonstrated the existence of specialized atrial pathways and the preferential pattern of atrial activation. Wittig et al.,[21] in their study of 38 patients with transposition of the great vessels, used intraoperative mapping of the atrial conduction system at various stages of Mustard's operation to demonstrate that no discrete intraatrial pathways exist. They found muscle bundles that are insulated from the surrounding atrial muscle and that are capable of conducting an impulse two to three times faster than areas of right atrial appendage. They concluded that block or delay in the two main (faster) pathways into the A-V node during atrial septectomy and baffle placement may compromise A-V nodal activation and facilitate atrial reentry and junctional escape rhythm. This contradicts the conclusion of Clarkson et al.[22] that preservation of the internodal pathways is of secondary consideration. However, only standard random electrocardiograms were analyzed in their postoperative study.

Atrioventricular nodal function: Our finding of normal A-V nodal effective refractory periods indicated normal A-V nodal function. This agrees with the data of Rodriquez-Fernandez et al.,[19] who found one of five patients with A-V node disease. None of Gillette's[4] patients had evidence of damage to the A-V node. Aberdeen et al.[23] demonstrated histologic evidence of acute and chronic inflammatory changes of the A-V node that were thought to be the genesis of postoperative complete heart block. Although complete heart block has been reported to occur, presumably due to damage to the A-V node during baffle placement, atrial arrhythmia and the "sick sinus syndrome" are more frequently encountered postoperatively.

Effect of atropine: Atropine has a chronotropic effect on the sinus node and enhances sinus nodal automaticity. This action is thought to be due to its vagolytic properties.[4–7] Our observations agree with those of Dhingra et al.[28] Sinus nodal recovery time was shortened in all but one patient and normalized in two patients after administration of atropine. Of the seven patients whose junctional pacemaker was the first to recover, one had conversion to sinus rhythm and normal sinus nodal recovery time after administration of atropine. This finding seems to support the hypothesis that atropine enhances sinus nodal automaticity and decreases S-A conduction time.

Controversy over the effect of atropine on atrial refractoriness still exists. Atropine had no consistent effect on the atrial effective refractory period in the patients studied by Akhtar et al.[27] However, Dhingra et al.[28] documented shortening of the atrial refractory periods in all of their 17 patients. We also found a decreased atrial effective refractory period in all of our patients after atropine, thus suggesting that atropine facilitates intraatrial conduction.

Results of Holter monitoring: Our study indicates that a 24 hour ambulatory electrocardiogram is superior to random electrocardiograms for arrhythmia detection. Had only standard electrocardiograms been obtained in our patients, the majority of rhythm disturbances would have remained undetected and the incidence of arrhythmia would have been underestimated. The standard random electrocardiogram is unreliable in assessing the integrity of the conduction system after Mustard's operation for transposition of the great vessels. This observation is supported by the results of a nation-wide survey of sudden unexpected death after Mustard's operation,[27] in which it was found that 15 (37 percent) of 41 patients who died suddenly, presumably from arrhythmia, manifested "sinus" rhythm in a standard electrocardiogram before death.

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Second Degree His-Purkinje Block During His Bundle Pacing

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This report presents, for the first time, clear evidence supporting the occurrence of Wenckebach and 2:1 H-V block during His bundle pacing. The simultaneous recording of various intracardiac electrograms, as well as the comparison of the effects produced by selective His bundle pacing and high right atrial pacing at the same rates, permitted the identification of conduction disturbances located distal to the paced His bundle site. This could be done although one criterion usually required to diagnose selective His bundle pacing (namely, stimulus-V intervals of *constant* duration) was not present.

The subject of His bundle pacing in the human heart has been a source of considerable debate and speculation.[1–9] For most authors,[1,3,6,7] the His bundle origin of a given deflection can be proved only if the QRS complexes and stimulus (St)-V intervals of paced beats have a constant duration that is similar to that of the ventricular complexes and H-V intervals of supraventricular beats. Thus, when dynamic His-Purkinje conduction disturbances are present during attempted His bundle pacing one of the most important criteria used for validation (St-V intervals of constant duration) will not be available. In these cases the St-V variations should resemble the H-V variations during sinus rhythm, as will be shown in this report. We believe that this is the first communication presenting clear evidence supporting the occurrence of second degree His-Purkinje block during His bundle pacing in the human heart.

Material and Methods

The technique used in our laboratory to record multiple intracardiac electrograms during atrial and ventricular stimulation has been discussed in previous communications.[9,10] After the procedure was explained and informed consent obtained, a tetrapolar electrode catheter was introduced through a femoral vein and positioned across the septal leaflet of the tricuspid valve to record a His bundle electrogram and a low septal right atrial electrogram from the vicinity of the atrioventricular (A-V) node. A hexapolar electrode catheter was introduced through an antecubital vein to record electrograms from the right ventricular apex (RVA),[9,10] mid right atrium (MRA) and high right atrium (HRA). Another, tetrapolar, electrode catheter was placed in the high right atrium approximately 15 to 25 mm from the high right atrial electrode pair of the hexapolar electrode catheter. Filtered (40 to 400 hertz and 400 to 500 hertz) electrograms were recorded simultaneously with three surface leads at a paper speed of 100 mm/sec. High right atrial and right ventricular apical pacing were performed at rates faster than that of the spontaneous sinus rhythm using a digital stimulator that delivered pulses of 2 msec duration and twice diastolic threshold. After completion of conventional atrial and ventricular stimulation studies (without changing the position of the hexapolar catheter electrode), pacing was performed through the bipolar electrodes from which His bundle activity had been recorded. Rectangular pulses 2 msec in duration and 5 milliamperes in intensity were used.

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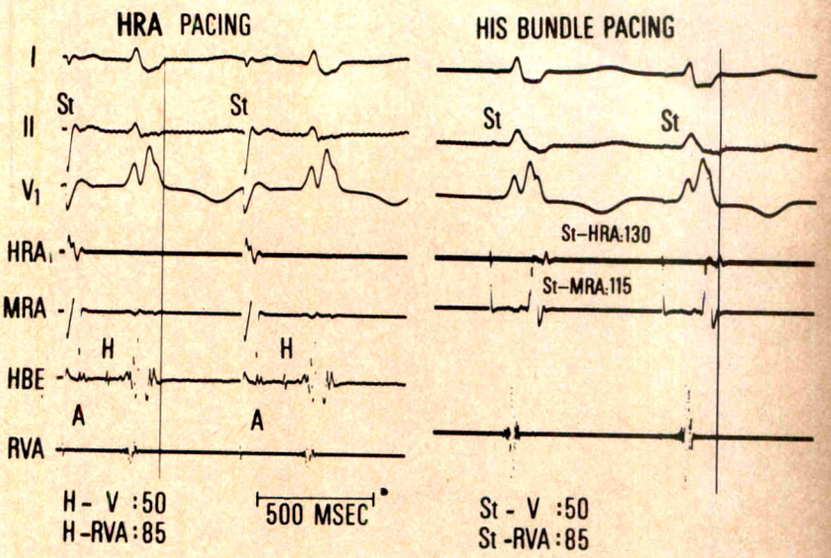


FIGURE 1. High right atrial pacing **(left)** and selective His bundle pacing **(right).** A = atrial electrogram; H = His deflection; HBE = His bundle electrographic lead; HRA = high right atrium; MRA = mid right atrium; RVA = right ventricular apex; St = stimulus artifact; V = onset of ventricular depolarization in the surface leads; I, II and V1 = surface electrocardiographic leads. In all figures, values are expressed in milliseconds.

Abbreviations are conventional except for V, which represented the onset of ventricular depolarization in the surface leads, because, for obvious technical reasons, a His bundle electrographic lead was not recorded during attempted His bundle pacing.

Case Report

A 62 year old woman with intermittent Wolff-Parkinson-White syndrome, recurrent supraventricular tachyarrhythmias, "complete" right bundle branch block and advanced atrioventricular (A-V) block in both (normal and accessory) pathways was referred for electrophysiologic evaluation. This report will deal only with findings pertinent to His bundle pacing. Other records from this patient relating to different electrophysiologic phenomena have been discussed elsewhere.[11]

Figure 1: The left panel shows the duration of the pertinent intervals measured during high right atrial stimulation at a cycle length of 560 msec, namely: A-H interval = 95 msec, H-V interval = 50 msec, H-RVA interval = 85 msec, St-H interval = 135 msec, MRA-H interval = 105 msec and QRS duration = 130 msec. During selective His bundle pacing (right panel) at a similar cycle length (550 msec) the St-V and St-RVA intervals and QRS complexes had the same duration as the ventricular complexes, H-V and H-RVA intervals shown during high right atrial pacing (left panel). Moreover, the St-HRA and St-MRA intervals (130 and 115 msec, respectively) were similar to the HRA-H and MRA-H intervals recorded when the high right atrium was stimulated (120 and 110 msec, respectively). This indicates that during selective His bundle pacing the atria were depolarized in retrograde fashion by the impulse that, after having been initiated at the His bundle, penetrated (and emerged from) the A-V node in a retrograde direction.

Figure 2: The St-HRA and St-MRA intervals were *shorter* (80 and 35 msec, respectively) when the His bundle was paced simultaneously with the low right atrium (left panel), and *longer* (205 and 160 msec, respectively) when right ventricular pacing resulted in retrograde (ventriculoatrial) conduction through the A-V node (right panel).[1,2,7,12]

Figure 3: The top panel shows 2:1 H-V block developing when the high right atrium was paced at a cycle length of 525 msec. In the bottom panel, obtained during selective His bundle pacing (cycle length 530 msec), all stimuli paced the His bundle and were conducted in retrograde manner to the atria through the A-V node. Thus the St-HRA and St-MRA intervals had the same duration as in the right panel of Figure 1. Moreover, every other stimulus was blocked distally to the

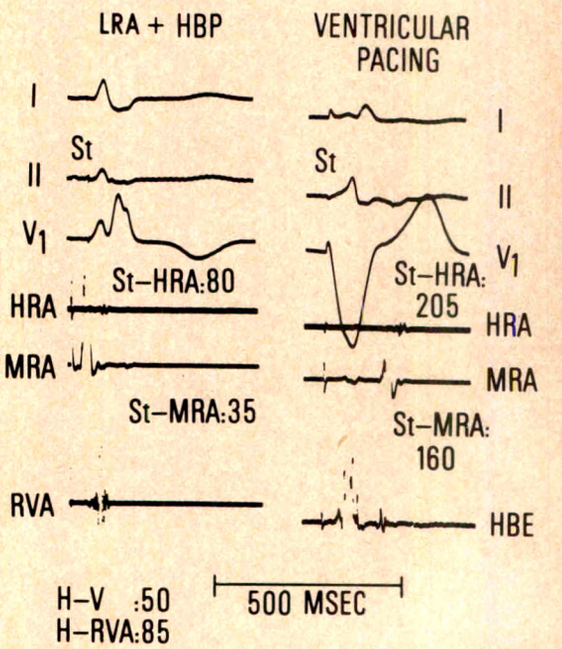


FIGURE 2. Combined low right atrial (LRA) and His bundle pacing (HBP) **(left)** and exclusive right ventricular apical pacing **(right)**. In comparison with selective His bundle pacing (Fig. 1, right), the corresponding (retrograde) St-HRA and St-MRA intervals were *shorter* during combined low right atrial and His bundle pacing and *longer* during ventricular pacing. Abbreviations as in Figure 1.

paced His bundle site. Hence, the blocked P waves (which in conducted beats were buried within the corresponding ventricular complexes) were clearly negative in lead II. The QRS complexes continued to show a pattern of "complete" right bundle branch block.

Figures 4 and 5: Previously, high right atrial pacing at cycle lengths of 550 to 540 msec had resulted in a 3:2 H-V Wenckebach phenomenon during which there was an increase in the H-V interval to 220 msec before the blocked impulse (Fig. 4). Furthermore, selective His bundle pacing at similar cycle lengths (Fig. 5) resulted (in addition to 1:1 retrograde conduction through the A-V node) in a 3:2 Wenckebach phenomenon occurring between the stimulated (His bundle) site and the ventricles. The St-V interval preceding the blocked impulse had a duration of 230 msec.

In summary, this patient with "complete" right bundle branch block manifested second degree H-V block (2:1 and Wenckebach) when the high right atrium and the His bundle were stimulated at similar cycle lengths. The conduction disturbance occurred in the low His bundle or in the left bundle.

Discussion

His bundle pacing has been considered the simplest, most direct and most reliable (and by some even the only) method available for validation of an H deflection.[1–3,6,7,12] Although these statements have been questioned on several grounds,[4,5,13] the simultaneous recording of several intracardiac electrograms has added another dimension to the understanding of the multiple

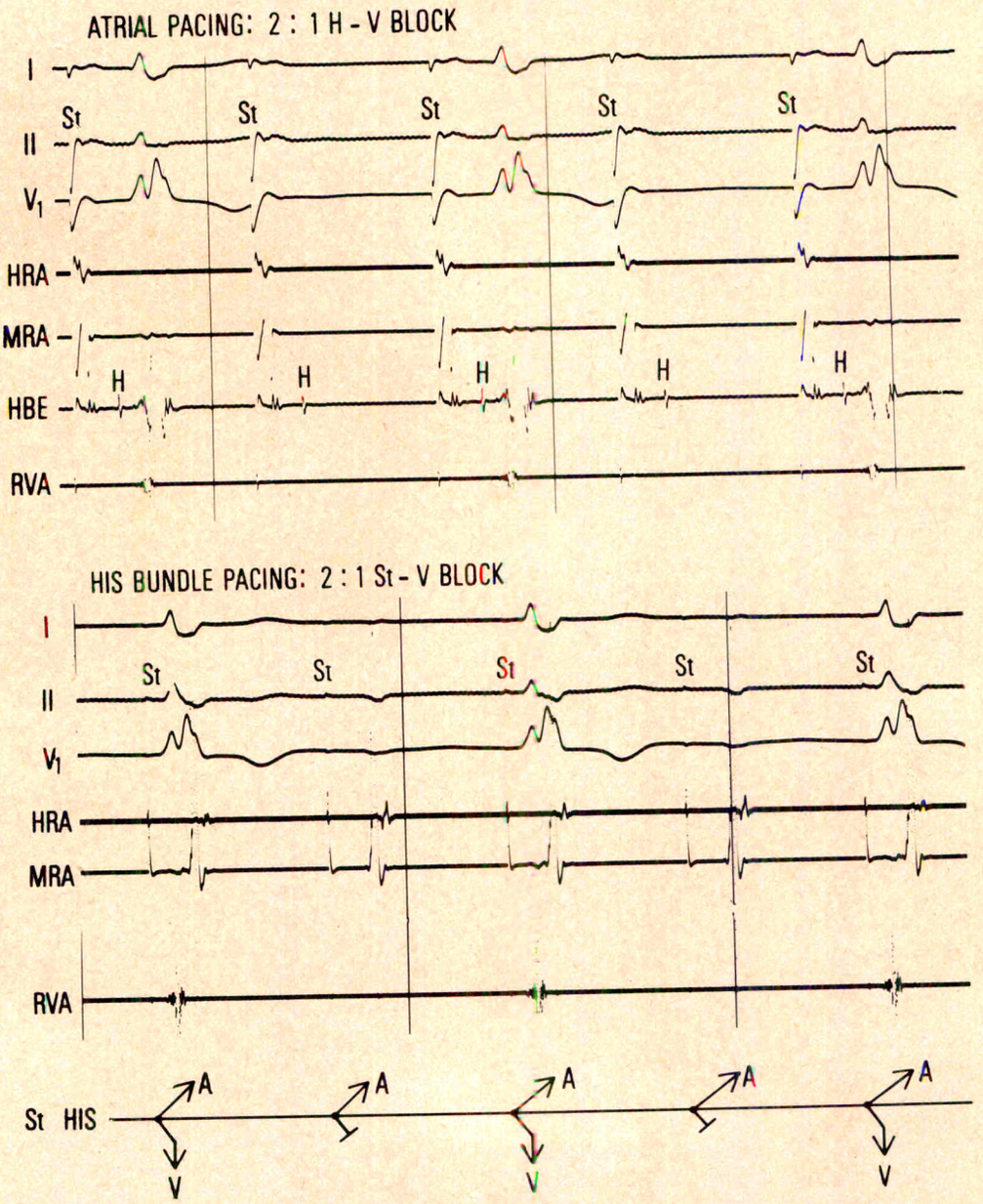


FIGURE 3. High right atrial (**top**) and His bundle (**bottom**) pacing showing 2:1 block in the "low" His bundle or left bundle branch. Intervals between time lines = 1,000 msec. Abbreviations as in Figure 1.

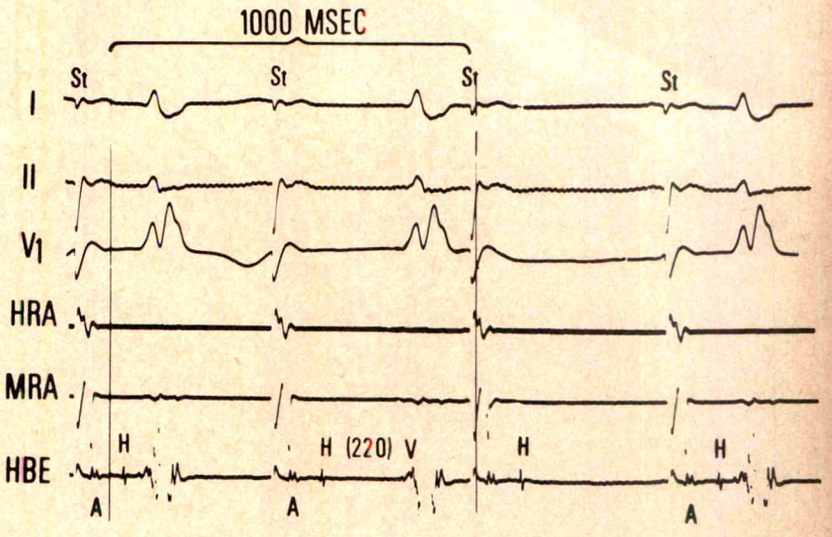


FIGURE 4. High right atrial pacing with 3:2 H-V Wenckebach phenomenon.

ventricular and atrial activation patterns that can be produced during attempted His bundle pacing in man. Thus, recording mid and high right atrial electrograms helped in the differentiation between selective His bundle pacing (Fig. 1, right), and combined His bundle and low right atrial pacing (Fig. 2, left). Conversely, recording of the right ventricular apical (RVA) electrograms permitted the application of a second criterion (in addition to the similarity between St-H and H-V intervals) for diagnosing His bundle pacing, namely, that the St-RVA interval be of the same duration as the H-RVA interval of supraventricular beats.[9]

However, it was the comparison between the effects produced by high right atrial and His bundle pacing at similar cycle lengths that gave the most useful information in this patient. The latter statement also applied to Case 4 of Narula et al.[1] These authors discussed the tracings of a patient who had A-V nodal Wenckebach block during atrial stimulation at a cycle length of 460 msec in whom His bundle pacing could be performed with a 1:1 response at even shorter cycle lengths (400 msec). The corresponding St-V intervals had a *constant* (*fixed*) duration (similar to the H-V intervals) because the block was *proximal* to the paced (His bundle) site. On the other hand, in Figure 5 of our case the St-V intervals had a duration that *varied* but was similar to that of the H-V intervals recorded during high right atrial pacing at similar cycle lengths. This occurred because the area of block (within the His-Purkinje system) was *distal* to the paced (atrial and His bundle) sites. In Figures 3 to 5, the conduction disturbances could have occurred in the "low" His bundle or in the left bundle branch.

On the other hand, in Case 1 of El-Sherif et al.[13] (with spontaneous intra-Hisian Wenckebach block), it was possible to perform His bundle pacing at rates higher than those at which H-V block developed. Presumably the block was located proximal to the paced site. Prolonged His-Purkinje times in the range recorded in our case (Fig. 4 and 5) were seen in the case of El-Sherif et al.[13] (H-V intervals progressively increased from 78 to 280 msec).

Moreover, Cohen et al.[15] reported on two patients with multiple complex Wenckebach block or alternating Wenckebach cycles in whom H-V intervals as long as 220 (Case 1) and 300 msec (Case 2) were recorded. Brusca et al.[14] studied a patient with second degree H-V block due to bilateral intermittent ("Phase 3") bundle branch block. Their Figure 3 was interpreted as showing H-V intervals ranging between 210 and 400 msec, this duration (presumably) being inversely related to the duration of the preceding H-H intervals.

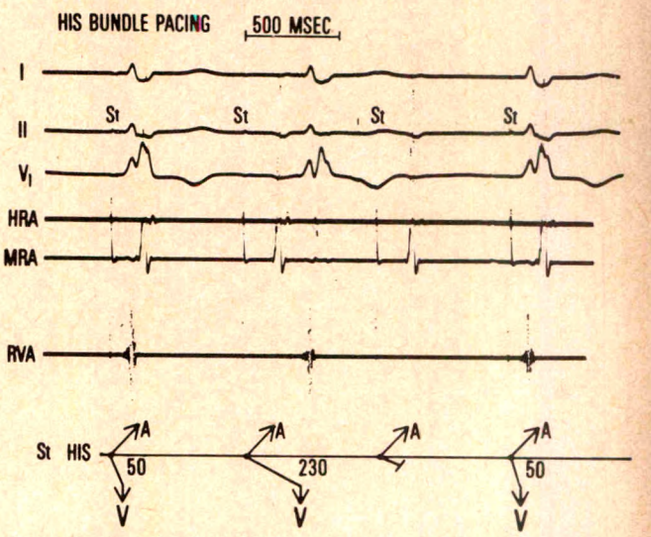


FIGURE 5. Selective His bundle pacing at a similar cycle length as in Figure 4 showing constant retrograde (1:1) conduction to the atria (through the A-V node) and anterograde 3:2 Wenckebach phenomenon occurring distal to the paced (His bundle) site. The behavior of the St-V intervals resembles that of the H-V interval in Figure 4. Abbreviations as in Figure 1.

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Atrioventricular Nodal Gap Conduction as a Manifestation of Dual Nodal Pathways

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Electrophysiologic studies were performed in a 76 year old patient for evaluation of sinus bradycardia. Atrial extrastimuli were induced during sinus rhythm at progressively decreasing coupling (A_1-A_2) intervals. At an A_1-A_2 interval of 420 msec, right bundle branch block developed, and at 370 msec conduction failed below the His bundle. When the interval was reduced to 320 msec, conduction resumed with a normal QRS pattern with an abrupt increase in A-H intervals from 165 to 305 msec. These findings are interpreted as type I or atrioventricular (A-V) nodal gap conduction physiologically related to conversion from a rapid to a slow A-V nodal conduction mode.

Intracardiac recording of electrocardiograms has permitted a more detailed understanding of many electrophysiologic events than was previously possible. Two phenomena defined using these techniques are "dual atrioventricular (A-V) nodal pathways"[1–4] and "gaps" in A-V conduction.[1,5–9] In the former, functional longitudinal dissociation of A-V junctional fibers results in a rapidly conducting path and a second slower tract. Which one conducts an incoming impulse relates to the differences in their refractory periods. In the second phenomenon, a lapse or "gap" in conduction occurs when impulses are presented within a narrow range of prematurity; conduction is intact with either longer or shorter coupling intervals. In the case to be described, both of these relatively uncommon features coexisted. A mechanism whereby the former leads to the latter is suggested.

Case Report

A 76 year old black man was referred for electrophysiologic evaluation because of persistent sinus bradycardia. The patient noted intermittent regular palpitations but was otherwise asymptomatic. He was not receiving any cardioactive medication. Physical examination was normal. Standard electrocardiograms demonstrated sinus bradycardia (rate 40 to 58/min) with a normal P-R interval, QRS duration and frontal plane axis. There was no evidence of ventricular preexcitation. A 24 hour electrocardiographic tape recording revealed only sinus bradycardia. Informed consent was given for electrophysiologic study.

Intracardiac recordings using two multipolar electrode catheters were obtained with the patient in a postabsorptive, unpremedicated state. Electrocardiograms were recorded after 40 to 500 hertz bandpass filtering. Atrial extrastimuli were coupled to normal sinus QRS complexes using a previously described microprocessor-controlled stimulator with software program logic.[10] Extrastimuli were introduced at coupling intervals of 555 to 100 msec at 25 msec decrements. Prematurity was quantitated by measuring the A_1-A_2 interval, that is, the interval from the last spontaneous atrial deflection (A_1) to the atrial deflection of the premature beat (A_2).

Results are presented in Figures 1 and 2. During normal sinus rhythm, the P-P, P-A, A-H and H-V intervals were 760, 30, 125 and 40 msec, respectively. The sinus rate remained stable to within 40 msec of the mean cycle length during the period of study. With A_1-A_2 intervals of 720 to 445 msec, A-V conduction remained normal with A-H times of 125 to 160 msec (Fig. 1A). At an A_1-A_2 interval of 420 msec, right bundle branch block occurred with an increase in H-V

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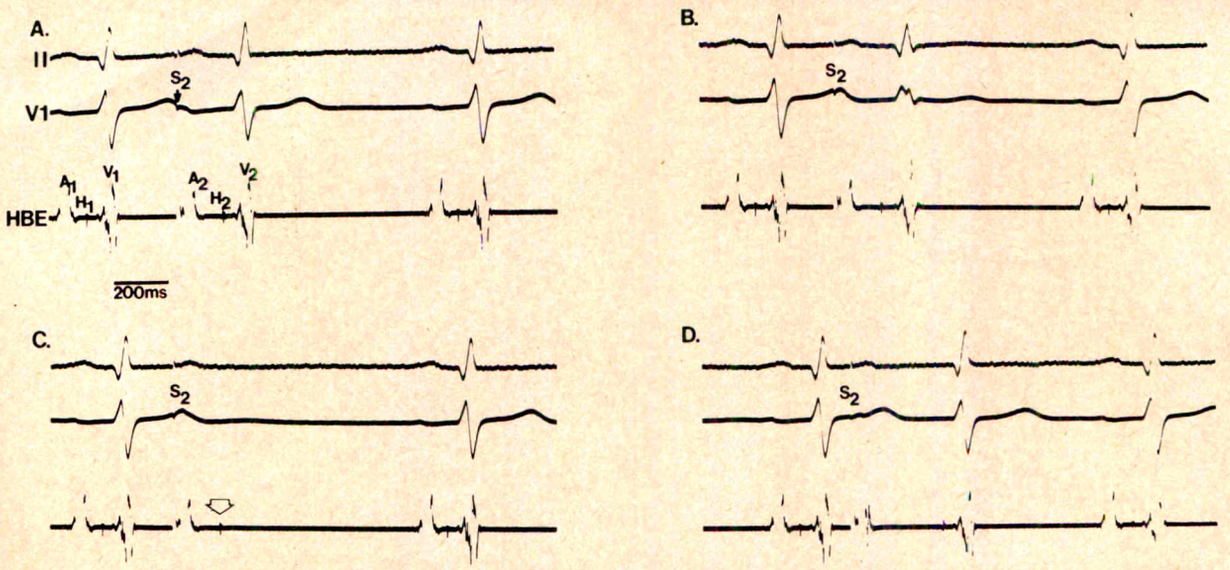


FIGURE 1. Representative cardiac cycles demonstrating the phenomena of dual atrioventricular (A-V) nodal pathways and A-V nodal gap. His bundle electrograms (HBE) are recorded simultaneously with standard leads II and V_1. **A,** at an atrial cycle length of 445 msec, A-V conduction is normal. A_1, H_1 and V_1 refer, respectively, to the atrial, His bundle and ventricular depolarization complexes induced by the sinus node. A_2, H_2 and V_2 identify atrial, His bundle and ventricular depolarization complexes, respectively, induced by a premature atrial stimulus, S_2. **B,** right bundle branch block with prolonged H-V conduction occurs at a coupling interval of 420 msec. **C,** the atrial extrastimulus is blocked below the His bundle recording site at an A_1-A_2 interval of 370 msec. The **open arrow** identifies the blocked His bundle response. **D,** at a coupling interval of 320 msec, A-H time increases to 305 msec from 165 msec **(C)** with resumption of conduction of the extrastimulus to the ventricles.

time of 60 msec (Fig. 1B). Further reduction in coupling resulted in block of conduction distal to the His bundle recording site (A_1-A_2 = 370, Fig. 1C). When coupling was still closer (A_1-A_2 = 320 msec, Fig. 1D), two phenomena were observed. First, the A-H interval abruptly increased to 305 msec. Second, conduction to the ventricles resumed with a normal QRS pattern and with a normal H-V time of 40 msec.

Plots of A_1-A_2 intervals versus A-V nodal conduction time and His bundle cycle lengths in the extrastimulus cycles (Fig. 2) revealed discontinuous curves. At a critical A_1-A_2 interval of 320 msec, A-V nodal conduction time increased abruptly, as did His bundle cycle length. No echo beats were recorded. Sinoatrial conduction time and corrected sinus nodal recovery time were normal.

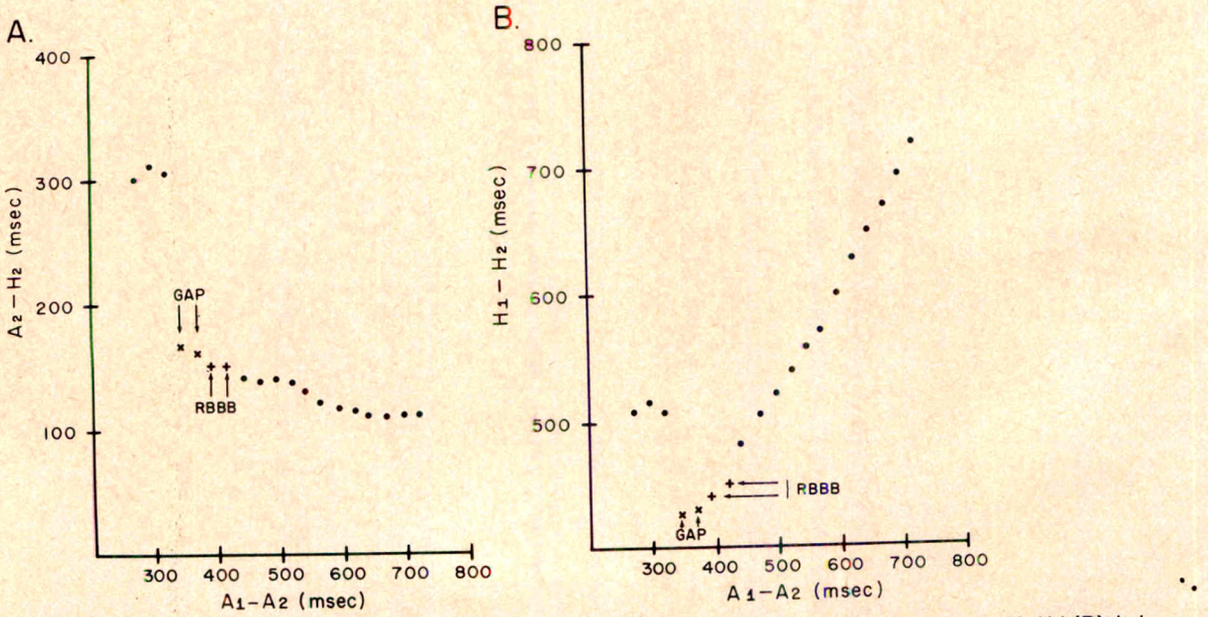


FIGURE 2. Plot of atrial cycle length (A_1-A_2) versus A-V nodal conduction times (A_2-H_2) **(A)** and versus His bundle cycle lengths (H_1-H_2) **(B)** during atrial extrastimulus testing. Beats conducted normally are identified by **closed circles,** beats conducted with a right bundle branch pattern are identified by a **plus sign** and nonconducted atrial beats are identified by a **cross.** RBBB = right bundle branch block.

Discussion

Dual A-V nodal pathways: The electrophysiologic data in this case support two diagnoses. First, the abrupt increase in A-V nodal conduction times at a critical coupling interval and the discontinuous coupling interval-conduction time plots (Fig. 2) suggest physiologic, and possibly anatomic, dual A-V nodal pathways.[1–4] Conduction time and His bundle cycle length increase suddenly with transfer of conduction from the relatively fast to the slower mode. Previously described manifestations of this pattern include echo beats, supraventricular tachycardias, atypical A-V nodal Wenckebach periods and a specific form of "supernormal" conduction.[4]

Other interpretations for the observed discontinuous curves may be proposed. For example, delay may be induced by arrival of a premature impulse during the relative refractory period of a portion of a single pathway.[11] The abrupt slowing of conduction, and hence the discontinuity in A-V conduction curves, may possibly represent conversion of propagation from a rapid, active mode to a slower, passive or electrotonic[12] mechanism within a single path. Another hypothesis is that the prematurity of the impulse causes it to engage only part of the A-V node, resulting in loss of the summation effects observed with total nodal activation; propagation velocity would then also decrease.[13]

A-V nodal gap phenomenon: A second diagnosis is that of type I, or A-V nodal, gap phenomenon.[1,5–9] In this pattern of conduction, impulses are blocked within the His-Purkinje system when their prematurity encroaches upon the effective refractory periods of these structures. As the coupling or A_1-A_2 interval is further decreased, the increased delay in propagation through the A-V node permits greater recovery times for the distal tissues, and conduction resumes. Thus, the cycle length observed by the His-Purkinje system increases despite a reduction in coupling intervals and atrial cycle lengths.

A-V nodal gap patterns are uncommon; for example, they were noted in only 6 of 45 subjects studied by Wit et al.[6] The necessity for the simultaneous occurrence of two unusual electrophysiologic phenomena may explain this infrequency. First, the effective refractory period of the His-Purkinje system must exceed the functional refractory period of the A-V node. Second, the A-V nodal conduction time must increase substantially without being totally blocked with relatively small increases in prematurity. This permits recovery of the distal tissues, thereby allowing conduction to continue.

In our case, block occurred sequentially in multiple areas of the His-Purkinje system. At an A_1-A_2 interval of 420 msec, right bundle branch conduction was significantly retarded[14] so as to produce an electrocardiographic pattern of right bundle branch block. The concurrent prolongation of the H-V time at this cycle length further suggests delay within the distal His bundle or left branch system.[15] When the coupling interval further decreased to 370 msec, corresponding to a His bundle cycle length of 430 msec, conduction below the His bundle recording site ceased. Finally, at a shorter A_1-A_2 interval of 320 msec but at a longer H_1-H_2 interval of 510 msec, A-V conduction resumed with a normal H-V time and QRS pattern.[8] This occurred as the A_2-H_2 interval abruptly increased from 165 to 305 msec, thought to result from transfer of A-V nodal conduction from a rapid to a slow transmission mode. Thus, the second requirement for gap conduction was provided by the coexistence of functionally dual A-V nodal pathways. Type I or A-V nodal gap may thus be considered an electrophysiologic consequence of dual A-V nodal pathways.

Mechanism: Durrer[5] proposed a mechanism whereby these two phenomena may be physiologically correlated. During normal conduction at long coupling intervals, conduction through high or junctional pathways occurs by way of the more rapidly conducting fibers. When prematurity increases and a gap in conduction is observed, the fast path is still used but the impulse reaches refractory tissue in the lower "final common" paths. Finally, conduction resumes as the effective refractory period of the fast system is reached and the impulse propagates through a slow path. The delay in reaching the final common pathway permits its recovery. This model is applicable to our case if one assumes the refractory site of the common path to be distal to the His bundle recording site.

Several other reported cases may be similarly interpreted. Wit et al.[6] demonstrated an abrupt increase in A-H times of premature atrial stimuli coincident with resumption of A-V conduction in a patient with a short P-R interval. This was attributed to conversion from a fast extranodal to a slower intranodal pathway at a critical coupling interval. In our case, an extranodal path was unlikely because the A-H times were normal at rest. Additionally, Damato et al.[7,9] reported cases of A-V nodal gap in which seemingly disproportionate increases in A-H times with small increases in extrastimulus prematurity led to resumption of A-V conduction. Thus, the occurrence of dual A-V conduction modes may not be an uncommon substrate for the recording of A-V nodal gap conduction patterns.

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Self-Initiated Conversion of Paroxysmal Atrial Flutter Utilizing a Radio-Frequency Pacemaker

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A patient is described with drug-resistant recurrent paroxysmal atrial flutter. Electrophysiologic studies demonstrated that flutter was inducible with rapid atrial stimulation (stimulation rates of 375 to 400/min) and convertible with rapid atrial stimulation (rates of 400 to 460/min). Because of the latter response, a radio-frequency atrial pacemaker was implanted, which allowed self-initiated conversion of flutter episodes with rapid stimulation.

Rapid atrial pacing has been utilized for successful conversion of atrial flutter. In previous reports, rapid atrial stimulation was performed utilizing temporary electrodes either in the catheterization laboratory or in the intensive or coronary care unit.[1–14] There is no previous study using rapid atrial pacing with a permanently implanted system for conversion of chronic recurrent paroxysmal atrial flutter.

In this report, we describe a patient with incapacitating recurrent paroxysmal atrial flutter in whom control of the arrhythmia was achieved with self-initiated rapid atrial pacing utilizing a radio-frequency pacemaker.

Report of Case

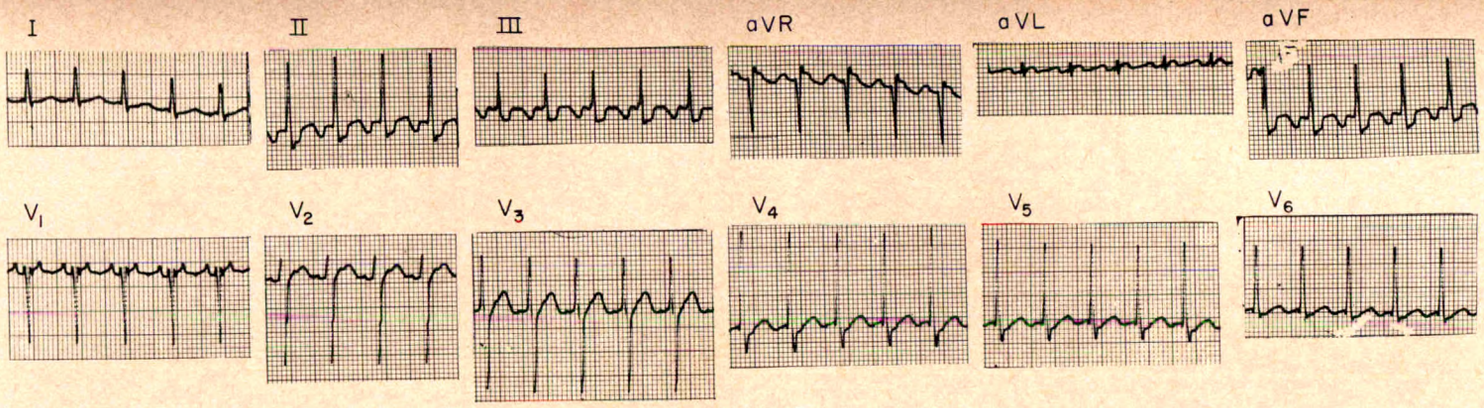
The patient, a 55 year old man with diabetes, was referred to the University of Illinois Hospital in October 1975 with a history of recurrent paroxysmal atrial flutter since 1964. Episodes of atrial flutter were accompanied by chest discomfort, dizziness, fatigue and sweating. Attacks had increased in frequency to approximately one to three per day since 1973, with most individual attacks lasting from 30 minutes up to 12 hours. The patient required 20 direct current cardioversions in 1975 for episodes lasting 12 to 48 hours and was forced to retire prematurely from work. Previous medications had included digoxin (up to 0.75 mg/day) and propranolol (up to 160 mg/day), without slowing of ventricular response or prevention of attacks. Quinidine (600 mg/day) produced intolerable diarrhea without preventing arrhythmia.

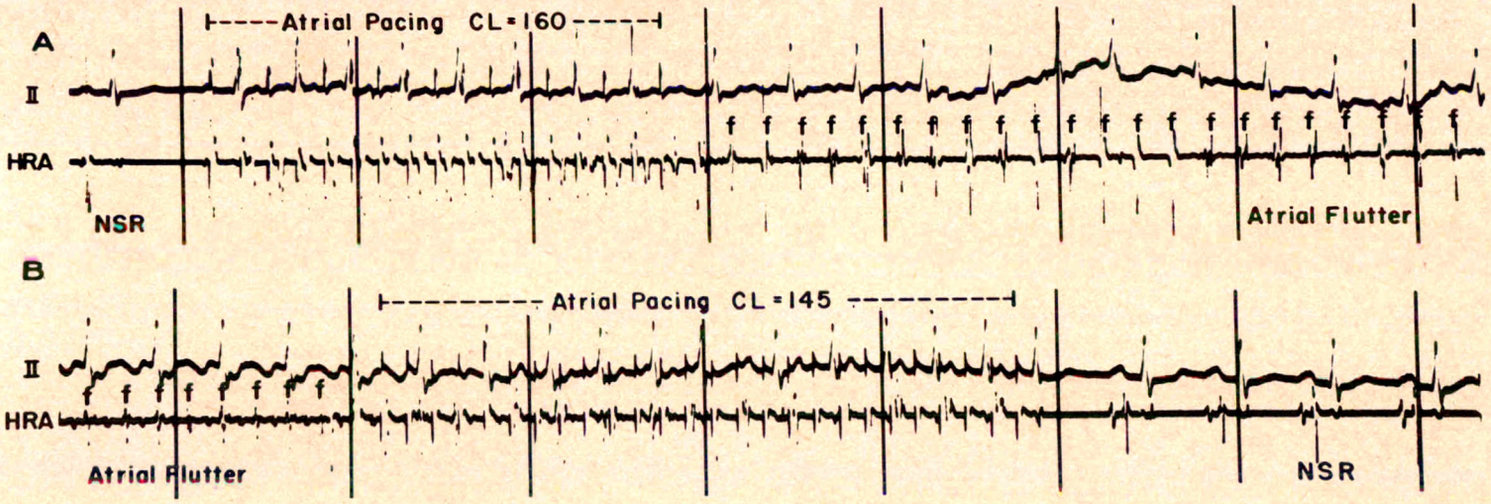
Physical examination was within normal limits. Electrocardiograms were within normal limits, except for sustained paroxysms of atrial flutter with 2:1 block (Fig. 1). Chest X-ray film, echocardiogram, treadmill exercise test, left ventriculogram and coronary angiograms were within normal limits.

Electrophysiologic studies were performed in November 1975, using a quadripolar electrode catheter placed in the high right atrium for right atrial recording and stimulation, and a tripolar catheter for recording of His bundle electrograms. A-H and H-V intervals were within normal limits (82 and 30 msec, respectively) during sinus rhythm at a cycle length of 660 msec. Rapid incremental atrial pacing resulted in atrioventricular (A-V) nodal Wenckebach periodicity at paced rates of 200/min and greater, and reproducible induction of sustained atrial flutter at paced rates of 375 to 400/min (Fig. 2A). Atrial flutter cycle length was 200 msec with 2:1 A-V conduction. Termination of atrial flutter, either directly to sinus rhythm or by way of brief nonsustained atrial fibrillation, occurred reliably after short bursts of atrial pacing at 400 to 460/min (Fig. 2B).

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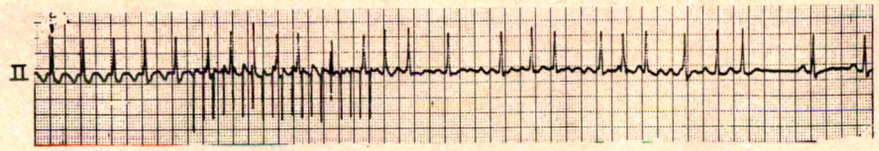


FIGURE 1 (top). Electrocardiogram showing typical atrial flutter with 2:1 atrioventricular response.

FIGURE 2 (center). Electrode catheter induction **(A)** and termination **(B)** of atrial flutter. Shown in each panel are lead II and a high right atrial electrogram (HRA). CL = paced cycle length (msec); NSR = normal sinus rhythm.

FIGURE 3 (bottom). Postoperative lead II rhythm strip showing atrial flutter, induction of radio-frequency–triggered atrial pacing at 470/min with atrial capture and conversion to normal sinus rhythm after nonsustained atrial fibrillation.

Implantation of radio-frequency pacing system: After initial study, the quadripolar catheter was left indwelling for high right atrial stimulation during subsequent daily intravenous drug trial. Atrial flutter was reliably induced both before and after intravenous administration of ouabain (0.75 mg), propranolol (7.5 mg) and procainamide (750 mg) on subsequent days. All induced episodes (as well as spontaneous episodes) of atrial flutter were readily converted to sinus rhythm with rapid atrial stimulation. Because of inability to define drug therapy that prevented induction of atrial flutter, a transthoracic bipolar radio-frequency pacing system (Medtronics model 1258) using pediatric plaque electrodes (Medtronics model 5815) attached to the anterolateral right atrium was implanted in December 1975. Bipolar stimulus threshold was 0.7 v at 1.3 milliamperes as measured with a Medtronics model 5300 pacing systems analyzer delivering a rectangular impulse of 1 msec duration. In the postoperative period, multiple episodes of atrial flutter were converted with radio-frequency atrial stimulation at a rate of 450/min to atrial fibrillation and then to sinus rhythm (Fig. 3). The patient was instructed in the use of the system and discharged 10 days later.

Subsequent course: The patient did well for 3 weeks, using the radio-frequency pacemaker for self-initiated conversion of atrial flutter approximately one to four times daily, activating the transmitter for 5 to 10 seconds at a rate of 450/min. However, within 2 weeks of discharge, sustained episodes of atrial fibrillation were induced, rather than immediate conversion of atrial fibrillation to sinus rhythm. The patient was again readmitted to the University of Illinois in January 1976.

With use of the radio-frequency pacemaker to induce flutter, it was easily demonstrated that both procainamide alone (3 g/day) and propranolol (160 mg/day) potentiated conversion of flutter to sinus rhythm by preventing induction of sustained atrial fibrillation. Oral propranolol, 160 mg/day, was given.

The patient was discharged in February 1976 and returned to full employment, using the radio-frequency pacemaker to convert atrial flutter to sinus rhythm approximately one to three times daily. In March 1977, the frequency of attacks increased, the patient having to use the pacemaker up to five to six times at night, and repeatedly during the day. Procainamide (2 g/day) decreased the frequency of attacks to two to four daily. The patient now uses his pacemaker two to four times daily and has had a beneficial effect from combined therapy designed to limit the frequency of attacks of atrial flutter (procainamide) and to limit the duration of pacing-induced atrial fibrillation (propranolol). He has now been followed up a total of 21 months since pacemaker implantation.

Discussion

This is the first reported case of reproducible induction of atrial flutter by rapid atrial stimulation (rates of 375 to 400/min) in a patient with known recurrent paroxysmal atrial flutter. The reproducible conversion (either directly to sinus rhythm or by way of atrial fibrillation) with rapid stimulation at rates of 400 to 460/min are consistent with previous reports using temporary electrode catheters. These electrophysiologic findings are most consistent with an atrial reentrant mechanism as a basis for flutter in this patient.[15]

Advantages of radiofrequency pacemaker system: The prior history of intractability to drug therapy, as well as the inability to define a drug that inhibited induction of flutter, suggested that an invasive mode of therapy would be indicated. In light of previous reports[16–22] of successful use of a radio-frequency pacemaker for self-conversion of paroxysmal supraventricular tachycardia, a radio-frequency pacemaker system was implanted with epicardial leads sutured on the right atrium. This system had the following advantages: (1) An external power source that was easily replaceable; (2) external control of atrial rate within a wide range; and (3) ability to initiate rapid stimulation by external control (by either physician or patient). The implanted system was then demonstrated to allow physician- and patient-initiated conversion of atrial flutter with rapid atrial stimulation. It is probable that other pacemaker systems allowing self-initiation of rapid atrial stimulation would have achieved identical results.

Although the system functioned adequately from the time of implantation, additional pharmacologic therapy was needed to achieve clinically satisfactory control of arrhythmia. Propranolol was demonstrated to prevent induction of sustained atrial fibrillation by the radio-frequency pacemaker. Procainamide was successfully used to decrease the frequency of attacks, necessitating less frequent use of the system.

Requirements for successful application of system: Use of the radio-frequency pacemaker requires that the patient be sufficiently well motivated to tolerate investigation involving repetitive arrhythmia induction and termination and also be sufficiently clinically disabled by the arrhythmia to justify this approach. Similarly, providing such a pacemaker to a patient is only practicable when the patient fully understands the working of the unit and when it should be used; that is, he should have some definite means of identifying the presence of the arrhythmia and be able to ascertain the presence or absence of sinus rhythm after use of the pacemaker. Successful use of the radio-frequency pacing system also requires extensive prior electrophysiologic studies and a full understanding of the nature and mechanism of the patient's arrhythmia. Furthermore, permanent pacing therapy is appropriate only when previous extensive trial has shown that the arrhythmia is resistant to several appropriate drugs, singly or in combination, or that drug toxicity has prevented pharmacologic control.

The general principle to be derived from our findings is that, in the management of a patient with a paroxysmal tachyarrhythmia that can be reliably and reproducibly induced and terminated by pacing techniques and for which extensive pharmacologic trial has proved unsuccessful, an external patient- or physician-controlled radio-frequency pacing system may provide a practical alternative mode of therapy.

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Paroxysmal Supraventricular Tachycardia: An Electrophysiologic Approach*

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The techniques of intracardiac recording and programmed stimulation have greatly expanded understanding of the mechanisms of supraventricular tachycardia and have resulted in a reclassification of these arrhythmias based on their electrophysiologic mechanism. Although several mechanisms of supraventricular tachycardia exist, the incidence and clinical features of each have not previously been evaluated systematically. The paper by Wu et al.[1] in this issue of the Journal is the first attempt to classify the electrophysiologic and clinical features of a large group of patients with paroxysmal supraventricular tachycardia without manifest anterograde preexcitation. As expected, reentry was the mechanism of supraventricular tachycardia in the vast majority of patients. Reentry could be localized to several sites including the sinus node, atrium, atrioventricular (A-V) node or a macroreentrant circuit involving the normal A-V conducting system in anterograde manner and a concealed A-V bypass tract in retrograde manner. As suggested in recent reviews,[2,3] Wu et al.[1] noted that the most common mechanism (69 percent) of supraventricular tachycardia was A-V nodal reentry. Significantly, the second most common cause (15 percent) was A-V reentry utilizing a concealed A-V bypass tract. In one patient with a concealed bypass tract, atrial stimulation from the coronary sinus, near the atrial insertion of the bypass tract, revealed that the bypass tract was able to function in an anterograde direction. Previous authors[4,5] have also recognized that A-V bypass tracts may not be evident in the surface electrocardiogram because of delayed or inadequate input into the bypass tract.

In a comparable group of 60 consecutive patients with supraventricular tachycardia and absence of anterograde preexcitation, we found a similar frequency of the cause of tachycardia: 66 percent had A-V nodal reentry and 20 percent had concealed A-V bypass tracts (unpublished observations). Two of the 12 patients with concealed bypass tracts manifested anterograde preexcitation during pacing from the coronary sinus. Thus, bypass tracts, clinically inapparent in the surface electrocardiogram, commonly form the retrograde limb of a reentrant circuit during supraventricular tachycardia and on occasion may be capable of anterograde conduction.

The electrophysiologic criteria used to establish the mechanisms of supraventricular tachycardia in the laboratory include: (1) mode of initiation of the tachycardia, with particular attention to the requisite site of conduction delay because slow conduction is a hallmark of the reentrant circuit; (2) atrial activation sequence and P wave contour during the tachycardia; (3) requirement of the atria or ventricles, or both, to initiate and sustain the tachycardia; (4) effect of bundle branch block on the tachycardia; (5) the effects of pharmacologic or physiologic maneuvers, or both, during the tachycardia; and (6) the effect of electrical stimulation during the tachycardia. Of these six observations only the last is inaccessible to the clinician.

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Many of the remaining observations are available from the surface electrocardiogram and can be used by the clinician to characterize the tachycardia. Although analysis of the surface electrocardiogram cannot provide as detailed and specific data as those obtained in the electrophysiology laboratory, a substantial amount of diagnostically important information is obtainable.

Observations at the Onset of the Tachycardia

If the clinician is fortunate enough to observe the onset of the tachycardia several important observations can be made. If the tachycardia is initiated (or, for that matter, terminated) by an early atrial or ventricular premature depolarization, reentry is the likely mechanism. Recent evidence has shown that under specific experimental conditions tachyarrhythmias can result when premature stimuli cause oscillatory afterpotentials to reach threshold.[6] These arrhythmias do not require conduction delay. However, the role of such "triggered automaticity" in tachycardia in man has not been established. Thus, if one can demonstrate that the initiation of the tachycardia by an atrial premature depolarization depends on achieving a critical degree of P-R prolongation, then the reentry must involve the A-V conducting system because this is the site of the conduction delay. This finding suggests that the mechanism of the tachycardia is either A-V nodal reentry or A-V reentry involving a concealed bypass tract. Neither sinus nodal reentry, intraatrial reentry nor automatic atrial tachycardia requires A-V delay for its initiation.

Analysis of the P wave configuration of the initial and subsequent beats of the tachycardia is also useful. If the P wave of the initiating atrial premature depolarization is identical to subsequent P waves during the tachycardia, automatic atrial tachycardia is likely.[7,8] In most cases of reentrant supraventricular tachycardia, the initiating atrial premature depolarization will not come from the same area that is depolarized by the impulse as it activates the atria after exiting the reentrant circuit. Finally, if an atrial premature depolarization initiates the tachycardia and the first atrial complex of the tachycardia is not conducted, then reentry utilizing a concealed bypass tract is ruled out and A-V nodal reentry becomes an extremely unlikely possibility. The basis for these conclusions is that (1) ventricular depolarization is necessary for the impulse to reach the ventricular insertion of the bypass tract, and (2) it is very difficult for reentry to be sustained in the A-V node in the presence of A-V nodal block.

Observations During the Tachycardia

Several important clues can be gleaned from the surface electrocardiogram during the tachycardia. Foremost among these are data obtained from the P wave configuration and the position of the P wave relative to the QRS complex during the tachycardia when the P wave is clearly seen. Thus:

1. Absence of a visible P wave during the tachycardia strongly suggests A-V nodal reentry because it implies simultaneous atrial and ventricular activation. This relation can occur only if the reentrant circuit is confined within the region of the A-V node. A similar relation can occasionally be noted during an automatic His bundle tachycardia. However this arrhythmia is most often nonparoxysmal and related to specific events such as digitalis toxicity, myocardial infarction or open heart surgery. The presence of a bypass tract functioning in retrograde manner is excluded because ventricular depolarization must activate the retrograde limb of the circuit (bypass tract) before the retrograde P wave can appear; thus, atrial and ventricular activation cannot be simultaneous.[9]

2. Inverted (retrograde) P waves in the inferior leads with an R-P interval less than one half the R-R interval are found in either A-V nodal reentrant supraventricular tachycardia (approximately 30 percent of patients with A-V nodal reentry) or reentry utilizing a concealed bypass tract (100 percent of these patients will demonstrate this pattern).[1]

3. Patients with retrograde P waves and long R-P intervals (R-P interval greater than one half the R-R interval) usually have an atypical, and often incessant, form of A-V nodal reentry.[10,11]

4. Patients with a P-R interval appropriate for the rate of tachycardia have either sinus nodal reentry, if the P wave is identical to the sinus P wave, or atrial tachycardia (automatic or reentrant), if the P wave is different from the sinus wave but not retrograde.[1,2,3,7]

In our patients with supraventricular tachycardia we found a greater incidence of concealed bypass tracts than that reported by Wu et al.[1] Approximately 50 percent of our patients with retrograde P waves and a short R-P interval during the tachycardia had concealed bypass tracts (unpublished observations). We have found the P wave configuration in lead I during the tachycardia helpful in analyzing the mechanism of the arrhythmia. We have found that a negative P wave in lead I, if discernible, is diagnostic of a left-sided bypass tract as confirmed with atrial mapping. Because the vast majority of patients with a concealed bypass tract have left-sided A-V connections, including all of Wu's patients and ours, a negative P wave in lead I assumes major diagnostic significance.

The relation of P waves to the QRS complex during the tachycardia provides another valuable diagnostic clue. In patients with concealed extranodal bypass tracts A-V block or A-V dissociation is impossible, and the presence of either rules out a concealed bypass tract because both the atria and ventricles are requisite components of the reentrant circuit. The presence of A-V dissociation with an atrial rate slower than the junctional rate has been reported with A-V nodal reentry[12,13] but is most commonly observed with nonparoxysmal junctional tachycardia. Sinus nodal reentry, automatic atrial tachycardia and intraatrial reentrant tachycardia may all exist in the presence of A-V block because neither the A-V node nor the distal conducting system is part of the reentrant circuit. On the other hand, A-V block is extremely uncommon in patients with A-V nodal reentry although a few cases of the lat-

ter, predominantly with infra-His block, have been reported.[9,13]

Functional bundle branch block is quite uncommon in supraventricular tachycardia except in tachycardias using a concealed bypass tract. As Wu et al.[1] noted, it is only in patients with the latter condition that the initiating atrial premature depolarization encroaches on His-Purkinje refractoriness resulting in bundle branch block. Bundle branch block is much less common in the presence of A-V nodal reentry because initiation of the tachycardia usually occurs during anterograde slow pathway conduction and thus the critical H_1-H_2 interval defining His-Purkinje refractoriness is not reached at the initiation of the tachycardia. We too have noted a similar large incidence of bundle branch block during tachycardias utilizing a concealed bypass tract. In our experience, aberration of the left bundle branch block type during supraventricular tachycardia has, with a single exception, occurred in patients with bypass tracts.

If both normal and aberrant conduction are observed in the same recording, a change in the cycle length of the tachycardia and R-P interval with the development of bundle branch block provides a diagnostic clue to the mechanism of the tachycardia. When supraventricular tachycardia utilizes a concealed bypass tract, bundle branch block ipsilateral to the side of the tract will prolong the cycle length of the tachycardia as a result of prolonged ventriculoatrial conduction time.[14] This occurs because the impulse must travel over the contralateral bundle branch, then through the contralateral ventricular muscle to the ventricular insertion of the bypass tract in the blocked ventricle. This produces a larger reentrant circuit and slower conduction within that circuit.

Pharmacologic and physiologic maneuvers can also be useful in determining the mechanism of the tachycardia. For example, the production of A-V block by carotid sinus pressure or other vagomimetic maneuvers with persistence of the tachycardia rules out the participation of the concealed bypass tract and makes A-V nodal reentry most unlikely. On the other hand, abrupt termination of a tachycardia by these maneuvers suggests that either the sinus node or the A-V node is involved; thus, one should consider a possible diagnosis of sinoatrial nodal reentry, A-V nodal reentry or A-V reentry utilizing a concealed bypass tract. As discussed, the P wave contour and its relation to the QRS complex during the tachycardia can help distinguish the former from the latter two mechanisms.

Therapeutic Implications of the Electrophysiologic Study

In patients with recurrent paroxysmal supraventricular tachycardia the electrophysiologic studies can provide major clinical benefits. Aside from establishing the mechanism of the tachycardia, such studies can aid in determining appropriate therapy.[15,16] Treatment of recurrent supraventricular tachycardia is often frustrating; multiple antiarrhythmic agents are often tried alone or in combination with a variable degree of both success and intolerable side effects. The ability to initiate and terminate predictably an arrhythmia provides the electrophysiologist with an *objective* means of assessing drug efficacy.

The methodology of such studies can be summarized briefly. After demonstrating that the tachycardia can be reproducibly initiated and terminated, a temporary electrode pacing catheter is left in the heart, and on sequential days multiple drugs are studied singly and in combination. At the end of this trial a single drug or drug combination that is most effective—that is, one that either prevents initiation or aids termination—is chosen for outpatient management. Thus the physician can choose on an objective basis the drugs most likely to be successful in the treatment of this arrhythmia.

Antiarrhythmic therapy needs to be individualized because patients with the same arrhythmia mechanism can respond differently to antiarrhythmic agents. This is of particular importance in patients with concealed bypass tracts, especially those in whom anterograde preexcitation can be produced with atrial pacing. Patients in whom anterograde conduction down the bypass tract can occur are susceptible to life-threatening ventricular responses during atrial flutter and fibrillation. In these patients digitalis, a drug often utilized successfully for various types of reentrant supraventricular tachycardias, may prove disastrous by producing A-V nodal block and decreasing bypass tract refractoriness, thus facilitating rapid conduction down the bypass tract resulting in ventricular fibrillation.[17,18] Patients potentially at risk for this complication can be identified from observations during the tachycardia. As noted in our laboratory and reported by Wu and others,[1,4,5,9,14] all patients with supraventricular tachycardia utilizing concealed bypass tracts have P waves after the QRS complex during the tachycardia. Thus, any patient whose P wave follows the QRS complex during supraventricular tachycardia, particularly when a negative component is noted in lead I, should probably undergo electrophysiologic testing.

In addition to determining the efficacy of various antiarrhythmic drugs, electrophysiologic studies can evaluate the potential therapeutic benefits of a pacemaker or surgery in the case of bypass tracts. In patients who are refractory to drugs, but in whom atrial or ventricular stimulation, or both, can terminate the tachycardia, permanent pacemakers, either atrial or ventricular, have been employed to terminate the arrhythmia on demand by the patient.[4,12,19,20] The arrhythmia is terminated when an appropriately timed impulse penetrates the reentrant circuit resulting in a collision of circulating wavefronts.

Who should undergo electrophysiologic study? Many electrophysiologists believe that patients with frequent recurrent episodes of paroxysmal supraventricular tachycardia, particularly those most likely to have concealed bypass tracts, should be evaluated with electrophysiologic studies. Such studies could avoid multiple readmissions or emergency room visits resulting from unsuccessful therapy. Furthermore, the ability to diagnose a free wall bypass tract through ex-

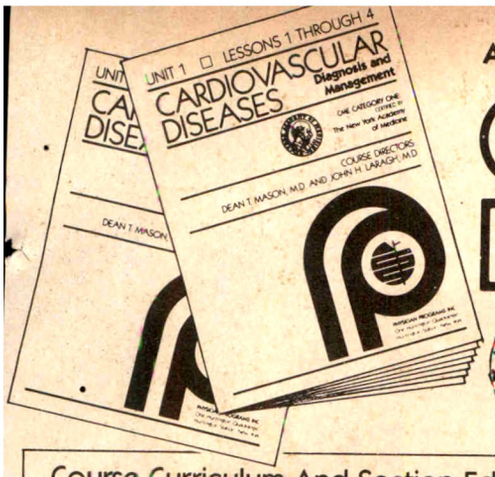
tensive electrophysiologic evaluation raises the possibility of surgically curing a disabling or life-threatening arrhythmia.[4] Both the extensive electrophysiologic evaluation and surgical therapy for arrhythmias should be done only in the centers that are best equipped and most experienced in these procedures. We have found such electrophysiologic evaluation invaluable in the management of patients referred with "intractable" supraventricular tachycardias. The therapeutic regimens selected on the basis of these studies have yielded rewarding results in 12 of 15 patients followed up for 6 to 15 months (unpublished observations).

Conclusion

Modern electrophysiologic techniques have permitted differentiatiation of the arrhythmia once called "paroxysmal atrial tachycardia" into several electrophysiologically distinct arrhythmias. The rational approach to therapy of an arrhythmia depends on knowledge of the mechanism of the arrhythmia. Certain clinical clues are available to help elucidate these mechanisms. They include P wave contour and the relation of the P wave to the QRS complex of the tachycardia, the presence of bundle branch block and its effect on the tachycardia and the effect of A-V dissociation on the tachycardia. Other clinical data, including the rate of tachycardia, incidence of organic heart disease and age and sex of the patient, are not specific enough to diagnose the mechanism of the arrhythmia, although patients with concealed bypass tracts do seem to be younger, have a lesser incidence of organic heart disease and tend to have faster rates of tachycardia.[1] It is in patients with recurrent disabling arrhythmias that electrophysiologic studies offer important data for making therapeutic decisions.

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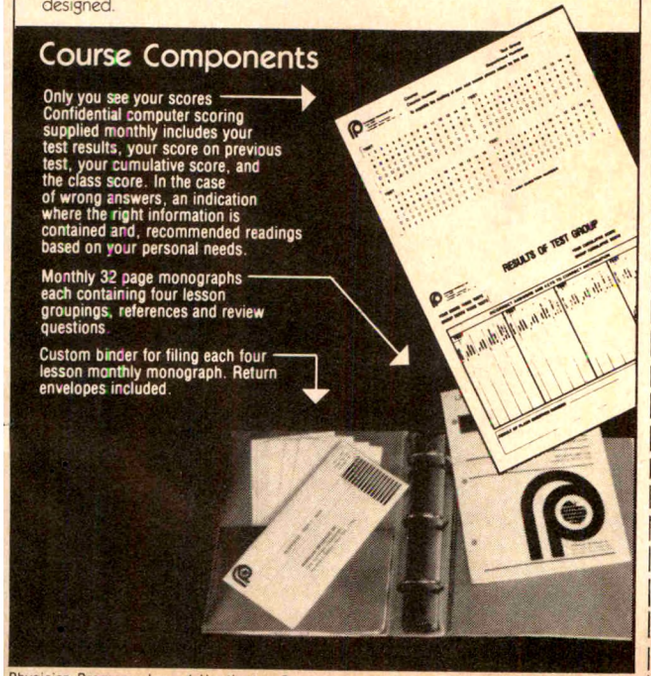
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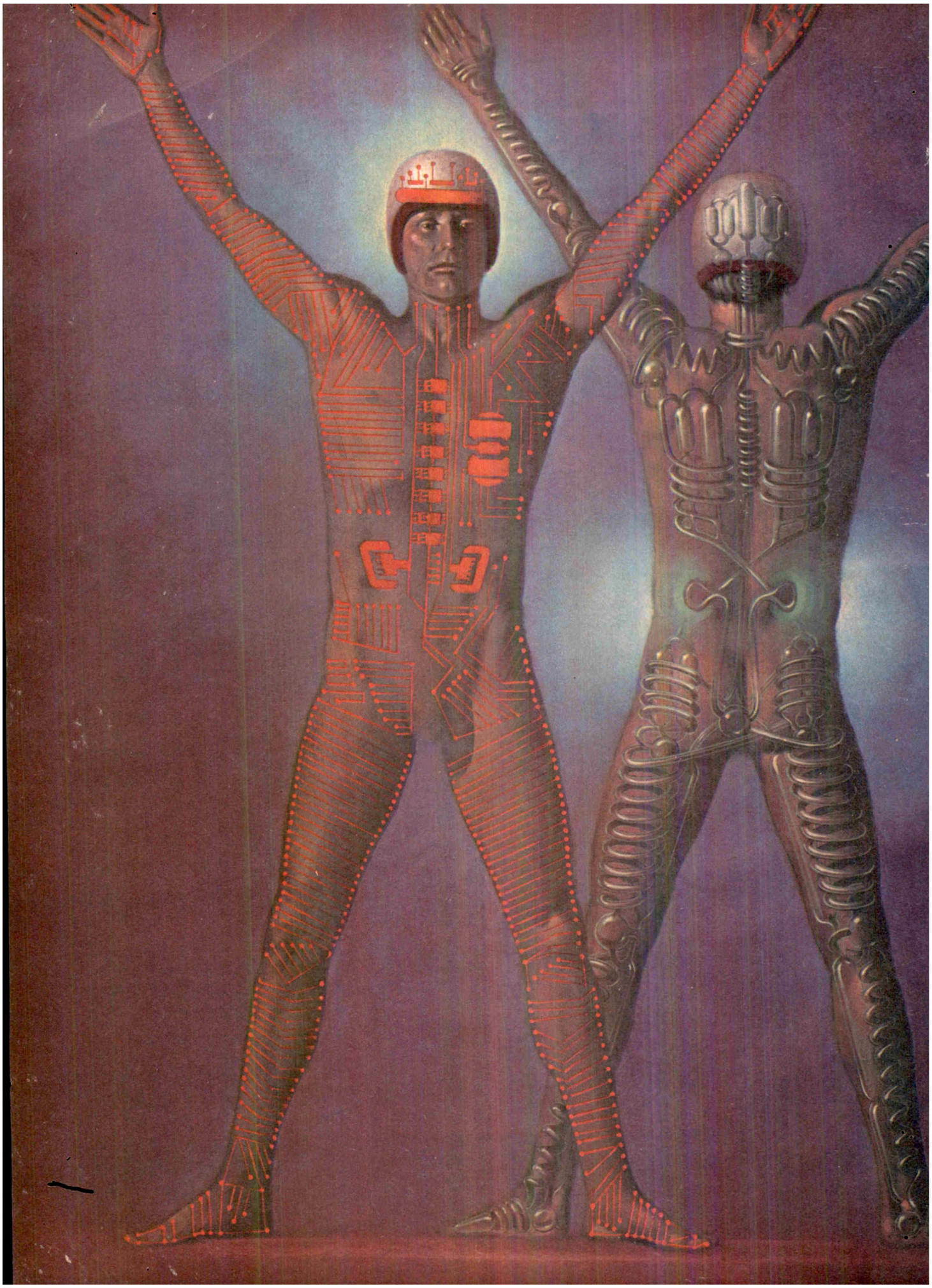
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Help your patient into the future

Combipres in hypertension

Combipres works efficiently, smoothly.
Brings blood pressure down...keeps it down over the long-term.

Life therapy...not life sentence

91% of patients tolerated it well in clinical trials.[1]
Low incidence of impotence, depression, orthostatic hypotension.
Its most common side effects are dry mouth, drowsiness, and sedation. They tend to diminish with continued use, and may be alleviated by giving the larger portion of the divided dose at bedtime.

Combipres® .1 and .2

Each tablet contains:
Catapres® (clonidine hydrochloride)
.0.1 or 0.2 mg. and chlorthalidone, 15 mg

There's a future in it.

Please see brief summary of the prescribing information on last page of this ad for warnings, precautions, and adverse reactions.

As with other antihypertensives containing diuretic agents, hypokalemia, hyperuricemia, and hyperglycemia may occur.

Combipres is not indicated for initial therapy of hypertension. See box warning on next page.

Combipres® .1 and .2

Each tablet contains:
Catapres® (clonidine hydrochloride) 0.1 or 0.2 mg, and chlorthalidone, 15 mg

in hypertension



...there's a future in it

Warning: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Indication: The drug is indicated in the treatment of hypertension (see box warning).

Contraindications: Patients with known hypersensitivity to chlorthalidone and patients with severe renal or hepatic diseases.

Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

A decreased glucose tolerance evidenced by hyperglycemia and glycosuria may develop inconsistently. This condition, usually reversible on discontinuation of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed should be checked regularly.

As with other diuretic agents hypokalemia may occur (see Precautions). Hyperuricemia may be observed on occasion and acute attacks of gout have been precipitated. In cases where prolonged and significant elevation of blood uric acid concentration is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Idiosyncratic drug reactions such as aplastic anemia, thrombocytopenia, leukopenia, agranulocytosis, and necrotizing angiitis have occurred, but are rare.

The remote possibility of pancreatitis should be considered when epigastric pain or unexplained gastrointestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reported with this general class of compounds include: jaundice, xanthopsia, paresthesia and photosensitization.

Overdosage: *Catapres (clonidine hydrochloride):* Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

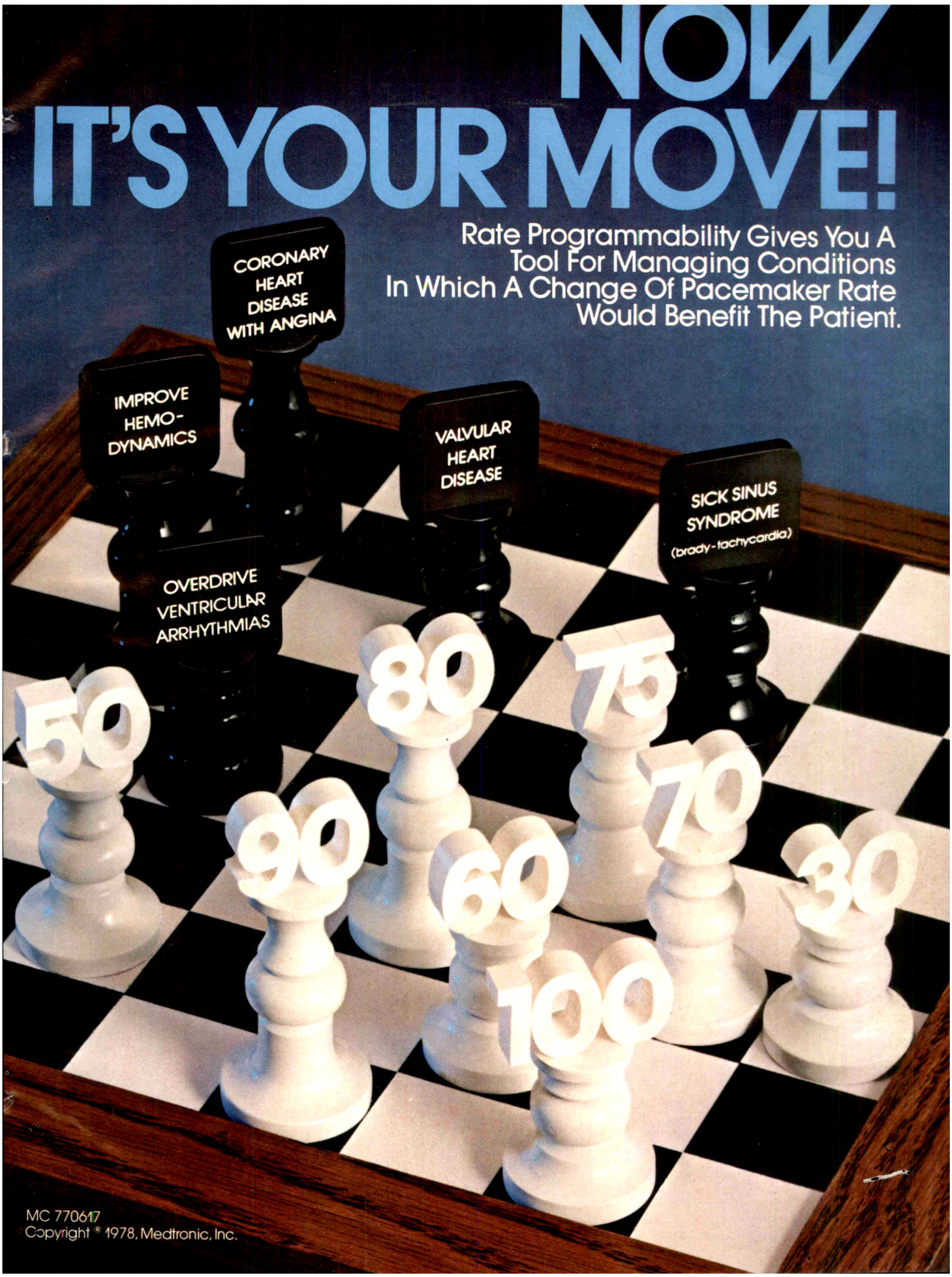
How Supplied: Combipres® 0.1 (Each tablet contains clonidine hydrochloride 0.1 mg + chlorthalidone,15 mg). It is available as pink, oval, single-scored compressed tablets in bottles of 100.

Combipres® 0.2 (Each tablet contains clonidine hydrochloride 0.2 mg + chlorthalidone,15 mg). It is available as blue, oval, single-scored compressed tablets in bottles of 100.

For complete details, please see full prescribing information.

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IT'S YOUR MOVE!
Rate Programmability Gives You A Tool For Managing Conditions In Which A Change Of Pacemaker Rate Would Benefit The Patient.
CORONARY HEART DISEASE WITH ANGINA
IMPROVE HEMO-DYNAMICS
VALVULAR HEART DISEASE
SICK SINUS SYNDROME (brady-tachycardia)
OVERDRIVE VENTRICULAR ARRHYTHMIAS
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THERE ARE AT LEAST FIVE APPLICATIONS IN WHICH HAVING THE FLEXIBILITY OF CHANGING PACED RATE CAN PROVIDE MORE VERSATILITY IN PATIENT MANAGEMENT.

These applications are:

1. Sick Sinus Syndrome (brady-tachycardia).
2. Coronary heart disease with angina pectoris.
3. Valvular heart disease.
4. To overdrive ventricular arrhythmias.
5. To improve hemodynamics.

In each of these, having the ability to change the pacing rate can preserve, maintain or improve the quality of life for pacemaker patients. Furthermore, because of the potential longevity of lithium pacemakers, the physician can take advantage of the greater flexibility provided by rate programmability to respond to the patient's changing medical condition during the pulse generator service life.



USING RATE PROGRAMMABLE PACEMAKERS IN CORONARY HEART DISEASE WITH ANGINA PECTORIS

Not infrequently, the patient in whom pacing is indicated presents with coronary artery disease and angina pectoris.

Angina may be occurring as a consequence of heart rate exceeding the ability of the coronary artery network to provide adequate circulation to myocardial tissue. Since heart tissues receive nutrients during diastole, it is felt that a slower heart rate and a corresponding longer diastolic period may provide enhanced opportunity for energy and oxygen transfer to myocardial tissue.

In any event, a rate programmable pacemaker permits evaluation for clinical symptoms at various rates and can permit selection of a pacing rate which is not likely to provoke angina, while providing the patient with adequate exertional status.





THE APPLICATION OF RATE PROGRAMMING IN BRADY-TACHYCARDIA (SICK SINUS SYNDROME).

After the physician has determined that artificial heart pacemaking is the treatment of choice for the patient with brady-tachycardia, he may contemplate application of a rate-programmable pacemaker to treat this disease.

Because brady-tachycardia may be a progressive disease, it is often appropriate to implant a rate-programmable pacemaker.

For example, in the early stages of the disorder, the patient may require pacing for just a few seconds a month when the intrinsic rate drops below a rate which the physician has determined provides adequate cardiac output. In such a situation, the pacemaker is set at a low rate (i.e., 50 or 60 ppm) to provide an underlying safe rhythm, but which allows the patient the benefit of his normal atrial ventricular contraction sequence.

Sick sinus syndrome at times is a progressive disorder which may result in a slowing of the patient's normal sinus rhythm. This slowing may be gradual or sudden. Frequently, it is accompanied by a tendency towards a more unreliable rhythm. The patient, thus, increases his or her reliance on the pacemaker for adequate heart rate.

Rate programming at increasingly higher rates may help maintain cardiac output at adequate levels when the pacemaker is needed to provide the dominant rhythm. An increase in pacemaker rate may also be needed to prevent the emergence of a less suitable tachyarrhythmia.



THE APPLICATION OF RATE PROGRAMMABLE PULSE GENERATORS IN VALVULAR HEART DISEASE

The clinical course for pacemaker patients with valvular heart disease is complex and unpredictable.

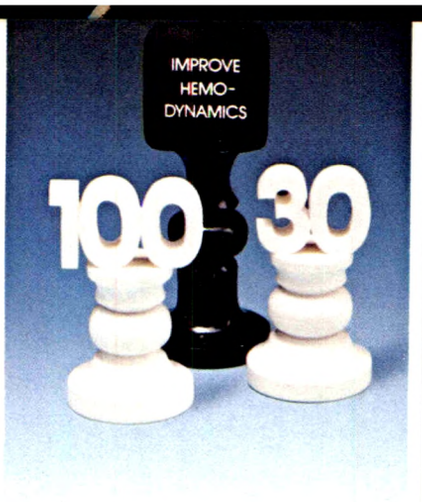
Many of these patients require a pacemaker prior to operation for their valve lesion.

The patient with aortic stenosis may need to have his rate adjusted to a slow level to allow for complete emptying of the ventricle. Too fast a rate increases ventricular pressure and restricts the flow of blood from the coronary arteries to the endocardium, resulting in subendocardial ischemia. There is some evidence that pacing at typical fixed pacemaker rates may actually cause patients with aortic stenosis to lose cardiac output and have decreased perfusion pressure.

On the other hand, the patient with aortic insufficiency has regurgitation backwards into the ventricle. A slow rate allows more blood to flow backwards, increasing volume and ventricular pressure. This also restricts blood flow from the coronary arteries to the endocardium, again resulting in subendocardial ischemia. A faster paced rate may help control the condition. Of course, the best rate for perfusing the endocardium for either condition varies considerably between patients.

Rate requirements will probably change a great deal when a prosthetic valve replacement is made.

Typically, any patient with valvular heart disease who requires a pacemaker could benefit from the flexibility a rate-programmable pacemaker offers in this complex, unpredictable disorder.



CHANGING RATE TO ENHANCE THE METABOLIC STATE THROUGH IMPROVED HEMODYNAMICS

Conditions of disease, or certain medical treatments, can affect a patient's metabolic requirements. Pacemaker patients are, because of their age and underlying heart disease, prone to various medical problems, including myocardial infarction, angina and congestive heart failure.

By having the ability to alter the diseased or ill patient's heart rate, the physician can optimize the rate for maximum cardiac output and organ perfusion without affecting (or with minor effects) on myocardial oxygen uptake. Also, in some MI patients a rate can be found which produces increased cardiac output with decreased left ventricular filling pressure. Rate changes may also affect and improve a patient's mental state and enhance the ability to perform even mild exercise. When a pacemaker is implanted, the patient is ill (i.e. bed-ridden). An adequate rate under those conditions may not be adequate when the patient is up and about.



USE OF RATE PROGRAMMABLE PACEMAKERS TO CONTROL VENTRICULAR ARRHYTHMIAS

Ectopic ventricular activity can be suppressed by permanent pacing. However, the slowest paced rate at which ventricular arrhythmias will be controlled is unpredictable, and changeable. It is not unusual for the rate at which PVC's occur to change as the patient's underlying heart disease progresses.

Pacing in the presence of PVC's often involves considerable adjusting of rate as the physician determines the paced rate which will be just slightly higher than the rate at which the ectopic foci discharge. This rate may involve a compromise, for an optimal rate for achieving maximal cardiac output may not coincide with the best rate for suppressing ectopic activity. Indeed some pacemaker rates tend to excite reentry pathways causing the extra-systole.

For these reasons, having the opportunity to change rate can assist the physician in arrhythmia control.

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Helping You
Help The Pacemaker Patient

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Offering you simplicity, ease of operation, and seven pacing rates plus one diagnostic rate for patient safety.

The Xyrel®-VP. It's as easy to program as 1, 2, 3.

1. Set the desired pacing rate.
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Constant Energy—A programmed pulse width increase as battery voltage declines provides for constant pacemaker energy output throughout its effective service life.

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*To avoid inadvertent programming to the 30 ppm rate, an additional step is necessary when this rate is desired.

Send in the coupon for details. Or see your local Medtronic representative.

MEDTRONIC IMPLANTABLE PULSE GENERATORS

INTENDED USES Ventricular pacing using an implantable ventricular pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation or conduction disorders leading to bradyarrhythmias, tachyarrhythmias and heart block (see product labeling for detailed list of intended uses).

CONTRAINDICATIONS There are no known contraindications to the use of pacing as a therapeutic modality for the control of heart rate. The patient's age and medical condition, however, may dictate the particular pacing systems and implantation procedure used by the physician.

WARNINGS Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of unipolar pulse generators or bipolar pulse generators implanted in the unipolar mode because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator.

PRECAUTIONS The physician should be aware that all pulse generators will ultimately cease to function, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, and elevated thresholds, and that proper operation may be affected by electrical interference from equipment using electrical energy, or medical complications.

SIDE EFFECTS Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.

MEDTRONIC HAS COMPILED MORE COMPLETE INFORMATION ON THE APPLICATIONS OF RATE PROGRAMMABILITY TO PACEMAKER PATIENTS

If you would like a copy of Medtronic's information guide on the applications of rate programmability where permanent ventricular pacing is indicated, please send in the coupon below.



Mail To: **Medtronic, Inc., 3055 Old Highway Eight, P.O. Box 1453 Minneapolis, MN 55440 USA**

- ☐ I would like more information on the applications of rate programmability.
- ☐ I would like more information on the Medtronic Xyrel®-VP programmable pacing system.
- ☐ Please have a representative call.

Name_____ Specialty_____

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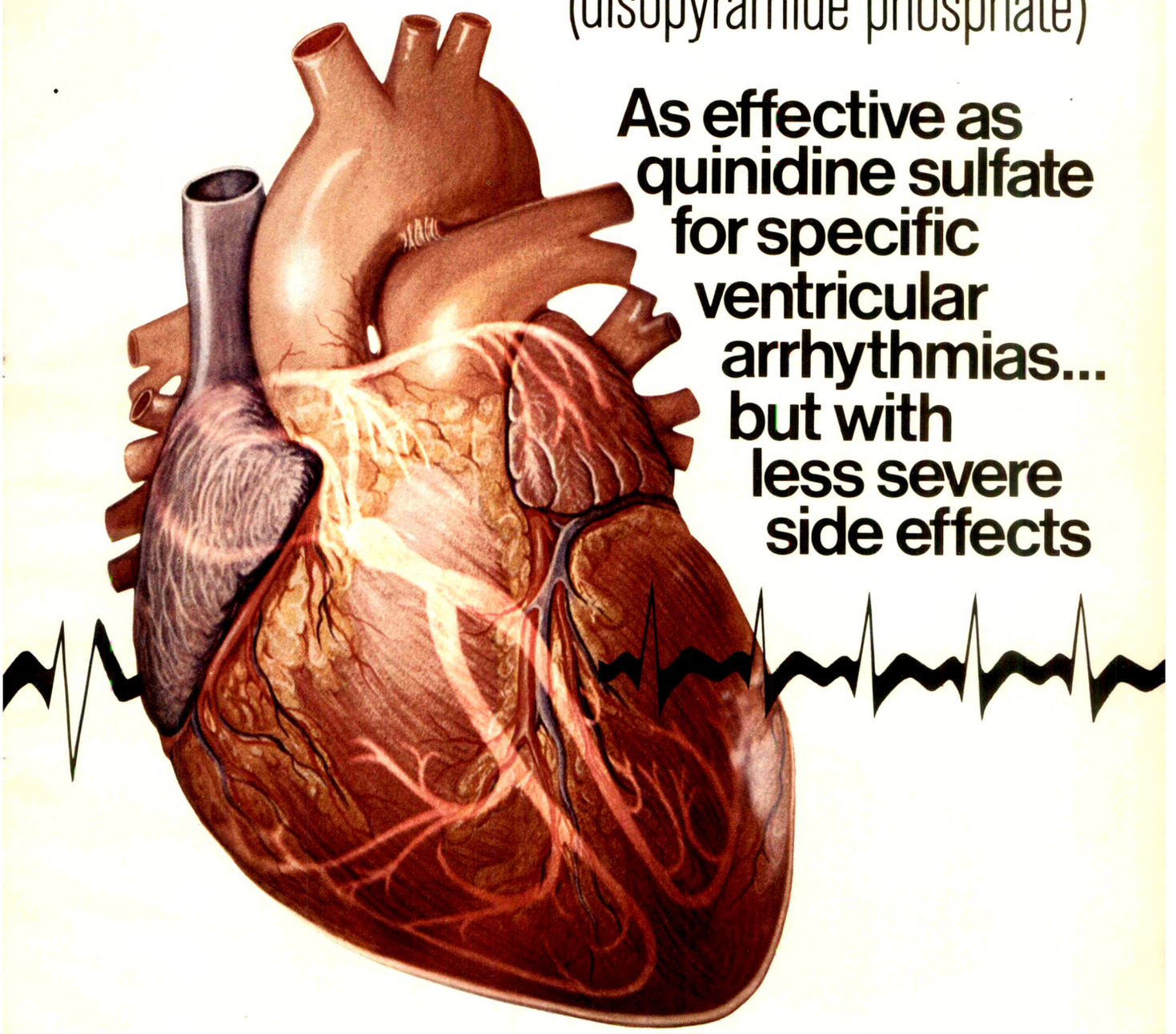
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Help The Pacemaker Patient.

From Searle

Norpace®

(disopyramide phosphate)



As effective as quinidine sulfate for specific ventricular arrhythmias... but with less severe side effects

Efficacy thoroughly proved and documented—no other antiarrhythmic agent subjected to such rigidly controlled study prior to introduction

Effective in specific ventricular arrhythmias—indicated in premature ventricular contractions (PVCs): unifocal, multifocal or paired PVCs or episodes of ventricular tachycardia (VT)

Excellent patient tolerance—less severe side effects than quinidine . . . and significantly better tolerated

Dose-related plasma levels—plasma levels correlate closely with dosage

Norpace effect on hemodynamics—rarely alters blood pressure significantly at recommended oral doses, and may reduce cardiac output by about 10%

Please see last page for a brief summary of prescribing information.

In specific ventricular arrhythmias...proved

Norpace®

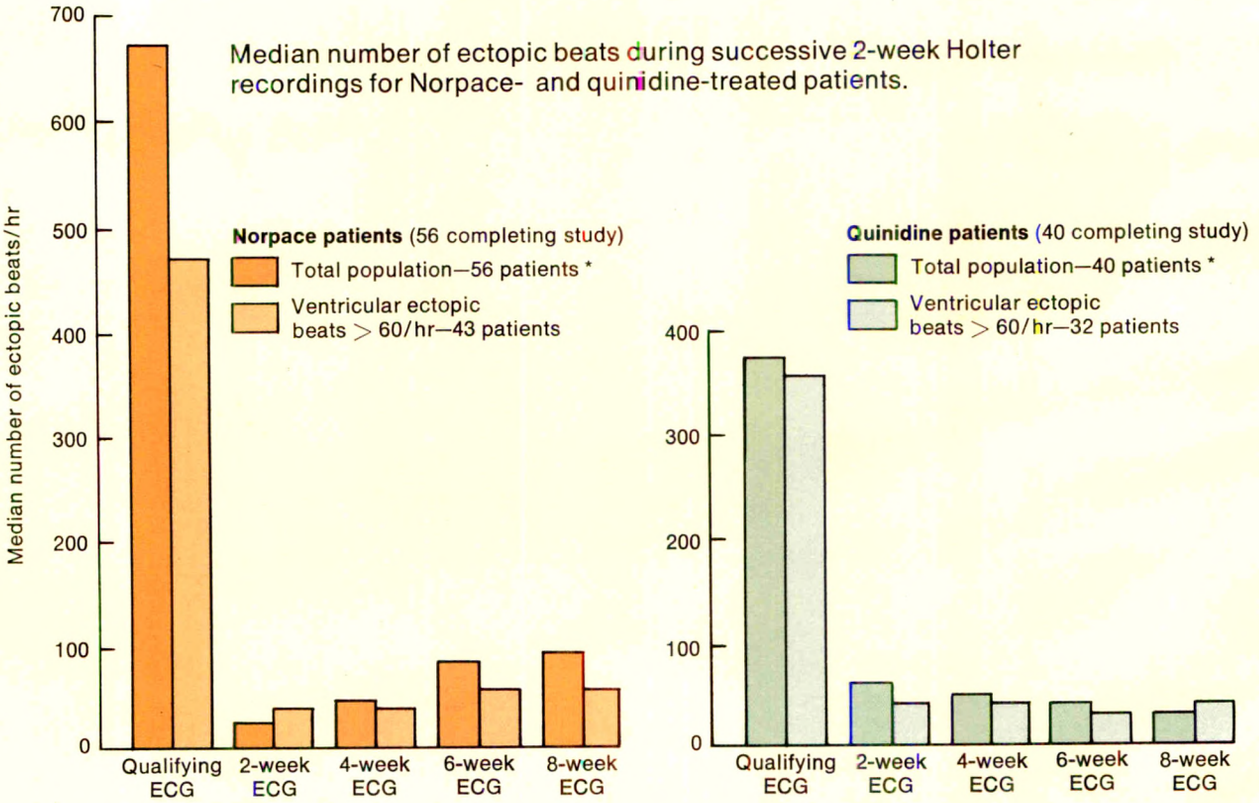
(disopyramide phosphate)

as effective as quinidine sulfate...

Results of double-blind controlled studies

A double-blind multicenter clinical study involving five investigators was conducted to compare the relative effectiveness and tolerance of Norpace and quinidine sulfate. Prior to qualifying for the study, each patient had antiarrhythmic medication discontinued for at least one week. Nine-hour Holter recordings were then used to establish an admission criterion of at least 60 ectopic beats per hour (PVCs, PACs or combination of the two). All other arrhythmias were excluded except paroxysmal ventricular or atrial tachycardias occurring in conjunction with the above. It was apparent that both drugs were capable of reducing ectopic activity and maintaining suppression throughout the course of therapy.

Median number of ectopic beats during successive 2-week Holter recordings for Norpace- and quinidine-treated patients.



* Includes patients with more than 60 total (atrial and ventricular) ectopic beats per hour but who had fewer than 60 ventricular ectopic beats per hour.

There was no statistically significant difference in reduction of ectopy between the two drugs.

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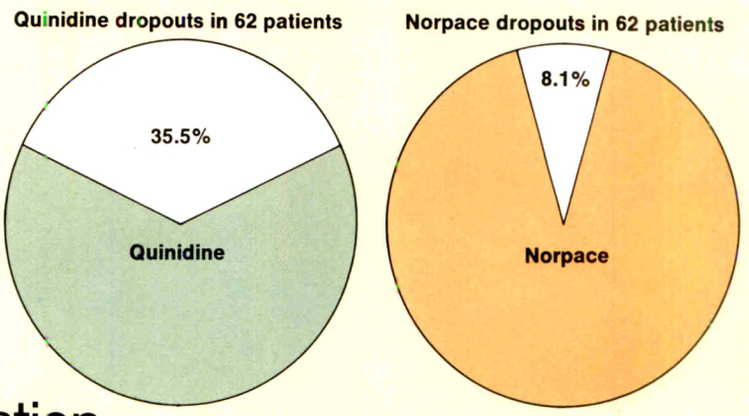
effective by extensive Holter monitoring

with less severe side effects

Significantly fewer dropouts with Norpace

(disopyramide phosphate)

The entire study population was analyzed for side effects. The side effects experienced by Norpace patients were usually mild and mainly anticholinergic, including: dry mouth, urinary hesitancy, constipation, blurred vision. The anticholinergic side effects were generally transient. Adverse reactions with quinidine were more serious and affected a greater number of patients. The most common symptoms were: severe diarrhea; gastrointestinal symptoms including cramps, nausea and vomiting; dizziness; fever; and rash.



Dosage and administration

Supplied as 100-mg and 150-mg capsules. Dosage should be individualized based on response and tolerance. Usual adult dosage is 400 to 800 mg per day given in divided doses four times daily.

Initial Norpace dosage

Patients 110 lb and over	150 mg q 6 h
Patients less than 110 lb	100 mg q 6 h
Patients with specific complications: Patients with *possible cardiac decompensation, cardiomyopathies, reduced left ventricular function* or *hypotension* due to these or other causes	100 mg q 6 h
Patients with moderate renal ($C_{cr} > 40$ ml/min) or hepatic insufficiency	100 mg q 6 h (200-mg loading dose optional)
Patients with severe renal insufficiency ($C_{cr} < 40$ ml/min)	100 mg given approximately every half-life (T½) (200-mg loading dose optional)
C_{cr} = 40–15 ml/min	q 10 h
C_{cr} = 15– 5 ml/min	q 20 h
C_{cr} = 5– 1 ml/min	q 30 h
In patients *without the complications* specified above in whom rapid control of arrhythmias is essential, therapy may be initiated with a loading dose of 300 mg (200 mg for patients under 110 lb).	

For complete Norpace dosage recommendations, please see full prescribing information, a brief summary of which appears on the next page.

SEARLE

Norpace®
(disopyramide phosphate)



as effective as quinidine sulfate for specific ventricular arrhythmias...with less severe side effects

Before prescribing Norpace (disopyramide phosphate), please consult current complete prescribing information, a summary of which follows:

Indications: Norpace is indicated for suppression and prevention of recurrence of the following cardiac arrhythmias when they occur singly or in combination: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion).

Norpace is equally effective in treating the above arrhythmias in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease. Oral Norpace has not been adequately studied in patients with acute myocardial infarction or in patients with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established.

Contraindications: Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug.

Warnings: Severe hypotension has been observed primarily in patients with primary cardiomyopathy or inadequately compensated congestive heart failure. If hypotension develops Norpace should be discontinued promptly unless hypotension is due to the arrhythmia.

Norpace should not be used in the presence of poorly compensated or uncompensated congestive heart failure unless it is exacerbated by or caused by an arrhythmia and proper treatment including optimal digitalization has been accomplished. In some patients with marginally compensated heart failure, Norpace may worsen cardiac decompensation. In these patients, progressing congestive heart failure should generally be treated with cardiac glycosides and diuretics and the course of treatment closely followed. Norpace dosage should be reduced or discontinued if adequate control of congestive failure is not attained.

If first-degree heart block develops, the dosage of Norpace should be reduced. If the block persists, continuation of Norpace must depend upon an assessment of the benefit versus the risk. Development of second- or third-degree AV block or uni-, bi- or trifascicular block requires discontinuation of Norpace, unless the ventricular rate is adequately controlled by a pacemaker.

Because of its anticholinergic properties, Norpace should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken.

Precautions: If significant widening (greater than 25%) of the QRS complex occurs, Norpace should be discontinued. If Q-T prolongation greater than 25% occurs and if ectopy continues, monitor closely and consider discontinuing Norpace.

Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits.

The effect of Norpace is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block.

Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of Norpace (disopyramide phosphate).

Norpace should be administered cautiously to patients who are receiving or who have recently received other antiarrhythmic drugs. Excessive widening of the QRS complex and/or prolongation of the Q-T interval may occur in such instances.

Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage.

Antiarrhythmic drugs may be ineffective in patients with hypokalemia. Therefore, any potassium deficit should be corrected before instituting Norpace therapy.

Use in Pregnancy and Lactation: Safe use in pregnancy has not been established. Norpace has been reported to stimulate contractions of the pregnant uterus. The use of Norpace in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus.

It is not known whether disopyramide is excreted in human milk. However, studies in rats have shown that the concentration of disopyramide and its metabolites is up to three times greater in milk than in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted.

Labor and Delivery: The effects of Norpace on the fetus during delivery or on the course of labor and delivery are unknown.

Pediatrics: The safety and effectiveness of Norpace in children have not been established.

Adverse Reactions: *Anticholinergic:* dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention. *Genitourinary:* urinary frequency and urgency. *Gastrointestinal:* nausea, pain/bloating/gas, anorexia, diarrhea, vomiting. *General:* nervousness, dizziness, general fatigue/muscle weakness, headache, malaise. *Cardiovascular:* hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain. *Dermatologic:* generalized rash/dermatoses. The following have occurred, but a causal relationship is uncertain: impotence, depression, insomnia, hypoglycemia, dysuria. Acute psychosis and cholestatic jaundice, both reversible, have been reported.

Dosage and Administration: Dosage must be individualized for each patient on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg per day given in divided doses four times daily. The recommended dosage schedule for most adults is 150 mg every six hours. For patients weighing less than 110 pounds (50 kg) the recommended dosage is 100 mg every six hours.

If rapid control of arrhythmia is essential, an initial loading dose of 300 mg of Norpace (200 mg for patients weighing less than 110 pounds) is recommended. For patients with cardiomyopathy or possible cardiac decompensation, a loading dose should not be given and the initial dose limited to 100 mg every six hours, with subsequent dosage adjustments made gradually under close monitoring.

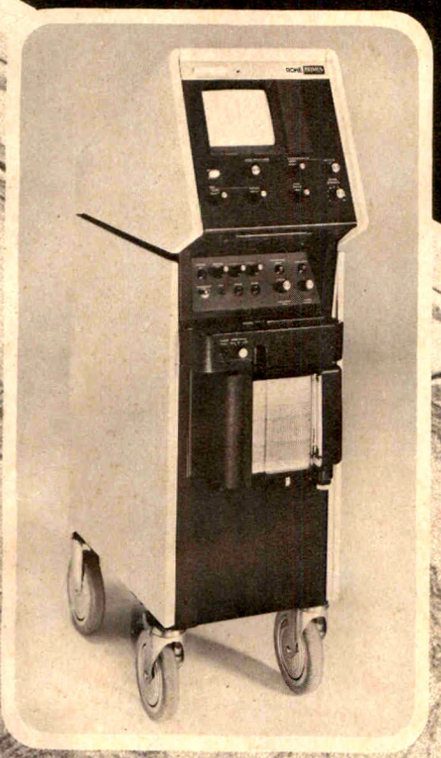
See current complete prescribing information for dosage recommendations.

How Supplied: Capsules containing 100 mg or 150 mg of disopyramide base. Available in bottles of 100 capsules.

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Searle Laboratories
Division of G. D. Searle & Co.
Box 5110, Chicago, Illinois 60680

7N2-R



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Most compact system offered with integral strip chart recorder

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Present

INAUGURAL INTERNATIONAL TEACHING CONFERENCE IN CARDIAC ARRHYTHMIAS

Tel-Aviv, Israel
October 22, November 1st., 1978

TOPICS: Basic mechanism of cardiac arrhythmias. Mechanism of action of antiarrhythmics. New techniques for the study of experimental and clinical arrhythmias. Atrialnodal, and ventricular reentry in man. Arrhythmias on mitral valve prolapse and myocardial infarction. Sudden arrhythmic deaths. Pre-excitation syndrome. **DISTINGUISHED INTERNATIONAL FACULTY:** Benjamin Befeler, M.D., U.S.A.; Philippe Coumel, M.D., France; Charles Fisch, M.D., U.S.A.; Guy Fontaine, M.D., France; Elieser Kaplinsky, M.D., Israel; Michael D. Klein, M.D., U.S.A.; H. E. Kulbertus, M.D., Belgium; Ronald Hope, M.D., U.S.A.; Ralph Lazzara, M.D., U.S.A.; K. I. Lie, M.D., The Netherlands; Henry Neufeld, M.D., Israel; Kenneth Rosen, M.D., U.S.A.; Mauricio Rosenbaum, M.D., Argentina; Lino Rossi, M.D., Italy; Benjamin Scherlag, Ph.D., U.S.A.; Libi Sherf, M.D., Israel; Shlomo Stern, M.D., Israel; Paul Touboul, M.D., France; Hein J. J. Wellens, M.D., The Netherlands; J. H. Yahini, M.D., Israel.

TRAVEL PACKAGE: (Teaching conference, air transportation, hotels and tours) $1400.00. Reduced fares for families. Advanced registration requested with deposit of $250.00 by July 15th. Departure from New York on Oct. 22nd. **HOTELS:** Tel-Aviv Sheraton (Oct. 23–29), Jerusalem Hilton (Oct. 29–Nov. 1). Benjamin Befeler, M.D., Program Director. **FOR RESERVATIONS AND INQUIRIES** Contact: **Cardiac Arrhythmias, c/o Leisure Time Tours, 18721 W. Dixie Highway., Miami, FL. 33180, or 305-931-8700 (Miami), 800-327-2044 (Outside Florida).**

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Sustained Action
(pentaerythritol tetranitrate) **80 mg**
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(pentaerythritol tetranitrate) **20 mg**
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CAUTION: Federal law prohibits dispensing without prescription.
Description: Each tablet of Peritrate SA Sustained Action contains: pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Each tablet of Peritrate 40 mg contains pentaerythritol tetranitrate 40 mg. Each tablet of Peritrate 20 mg contains pentaerythritol tetranitrate 20 mg. Each tablet of Peritrate 10 mg contains pentaerythritol tetranitrate 10 mg. Peritrate (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg and Peritrate (pentaerythritol tetranitrate) are contraindicated in patients who have a history of sensitivity to the drug.
Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.
This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.
Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.
Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe, persistent headaches may occur.
In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:
(a) Cutaneous vasodilatation with flushing.
(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.
(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.
Dosage: Peritrate (pentaerythritol tetranitrate) may be administered in individualized doses up to 160 mg a day. Dosage can be initiated at one 10 mg or 20 mg tablet q.i.d. and titrated upward to 40 mg (two 20 mg tablets or one 40 mg tablet) q.i.d. one-half hour before or one hour after meals and at bedtime. Alternatively, Peritrate Sustained Action 80 mg can be administered on a convenient b.i.d. dosage schedule.
Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg—double-layer, biconvex, dark green/light green tablets in bottles of 100 (N 0047-0004-51) and 1000 (N 0047-0004-60). Also unit dose, package of 10 x 10 strips (N 0047-0004-11).
Peritrate (pentaerythritol tetranitrate) 40 mg—pink scored tablets in bottles of 100 (N 0047-0008-51).
Peritrate (pentaerythritol tetranitrate) 20 mg—light green, scored tablets in bottles of 100 (N 0047-0001-51) and 1000 (N 0047-0001-60). Also unit dose, package of 10 x 10 strips (N 0047-0001-11).
Peritrate (pentaerythritol tetranitrate) 10 mg—light green, unscored tablets in bottles of 100 (N 0047-0007-51) and 1000 (N 0047-0007-60).
STORE BETWEEN 59° and 86° F (15° and 30° C).
Animal Pharmacology: In a series of carefully designed studies in pigs, Peritrate (pentaerythritol tetranitrate) was administered for 48 hours before an artifically induced occlusion of a major coronary artery and for seven days thereafter. The pigs were sacrificed at various intervals for periods up to six weeks. The result showed a significantly larger number of survivors in the drug-treated group. Damage to myocardial tissue in the drug-treated survivors was less extensive than in the untreated group. Studies in dogs subjected to oligemic shock through progressive bleeding have demonstrated that Peritrate (pentaerythritol tetranitrate) is vasoactive at the postarteriolar level, producing increased blood flow and better tissue perfusion. These animal experiments cannot be translated to the drug's actions in humans.
Full information is available on request.

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*This drug has been evaluated as possibly effective for this indication.
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Congestive Heart Failure

Mechanisms, Evaluation and Treatment

Dean T. Mason, M.D.



448 PAGES, 250 ILLUS./1976

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About the author . . . Dean T. Mason, M.D.

Professor of Medicine, Professor Physiology, Chief of Cardiovascular Medicine, University of California, School of Medicine, Davis

President, American College of Cardiology President, Western Society for Clinical Research

Member of the American Board of Internal Medicine Cardiovascular Diseases

Has authored more than 400 original articles on cardiovascular science and clinical cardiology.

Serves on the editorial boards of The American Journal of Cardiology, The Journal of Clinical Investigation, Circulation, Chest, Clinical Pharmacology and Therapeutics, Catheterization and Cardiovascular Diagnosis, and Heart and Lung.

Recipient of Experimental Therapeutics Award in 1973 from the American Society of Pharmacology and Experimental Therapeutics, the Research Awards in 1965 from the American Therapeutic Society, and the Theodore and Susan B. Cummings Humanitarian Awards in 1972, 1973, and 1975 from the U.S. State Department and the American College of Cardiology.

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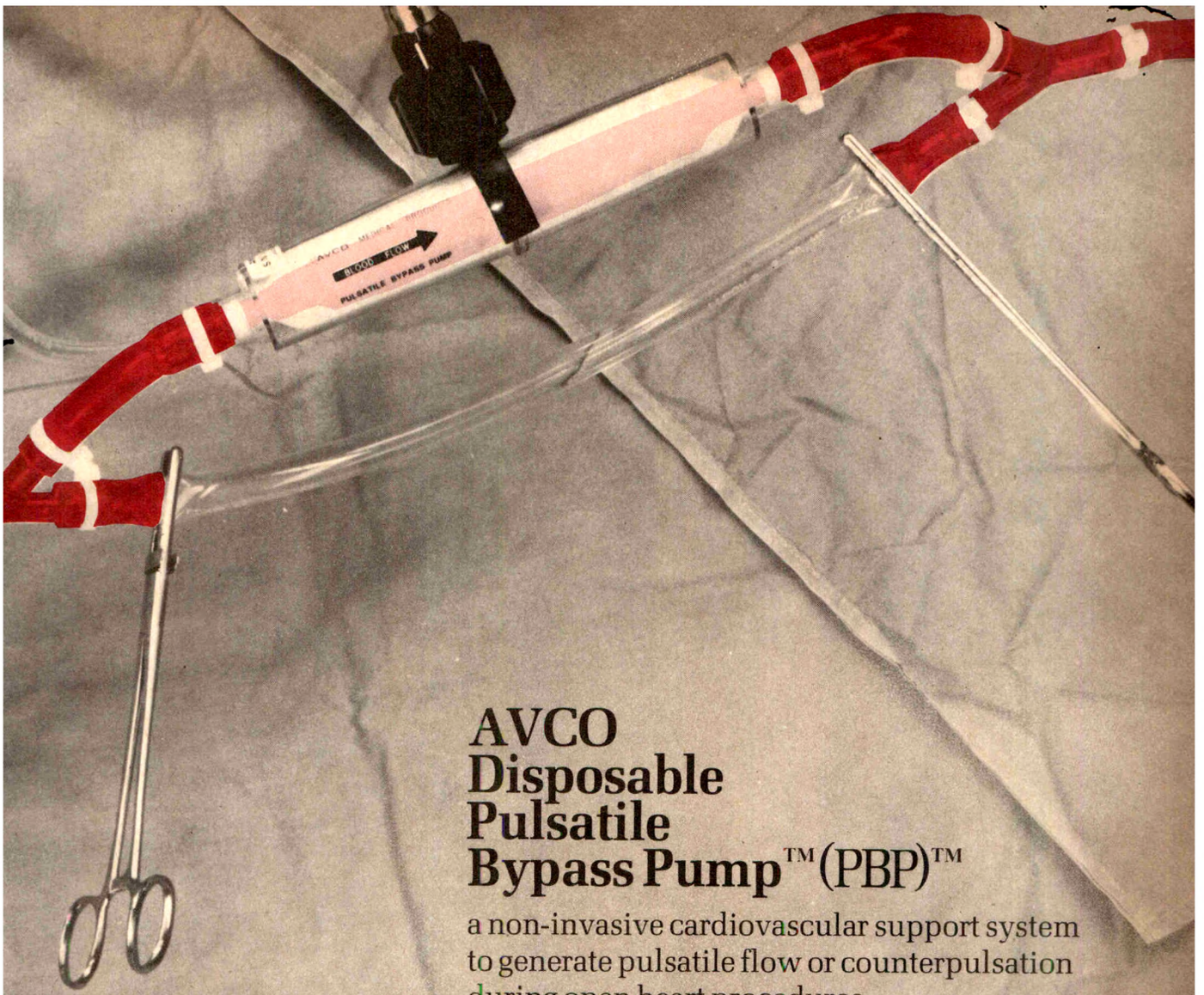
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12. Nature and Significance of Alterations in Myocardial Compliance — J.W. Covell.
13. Renal Function and Edema Formation in Congestive Heart Failure — M.J. Tonkon, S.M. Rosen and D.T. Mason.

II. Evaluation

14. Physical Findings in Heart Failure and Their Physiologic Basis — R.A. O'Rourke and M.H. Crawford.
15. Echographic Evaluation of Cardiac Function — A.N. DeMaria, A.L. Neumann and D.T. Mason.
16. Cardiac Catheterization in the Clinical Assessment of Heart Disease and Ventricular Performance—D.T. Mason, R.R. Miller, D.S. Berman, L.A. Vismara, D.O. Williams, A.F. Salel, A.N. DeMaria, H.G. Bogren, G.L. DeNardo and E.A. Amsterdam.
17. Catheterization Evaluation of Cardiac Function in Acute and Chronic Coronary Artery Disease — C.E. Rackley, R.O. Russell, Jr., R.E. Moraski, J.A. Mantle, B.J. Feild and M. Smith.

III. Treatment

18. Management of Chronic Refractory Congestive Heart Failure—D.T. Mason, R.R. Miller, D.O. Williams, A.N. DeMaria, L.D. Segel and E.A. Amsterdam.
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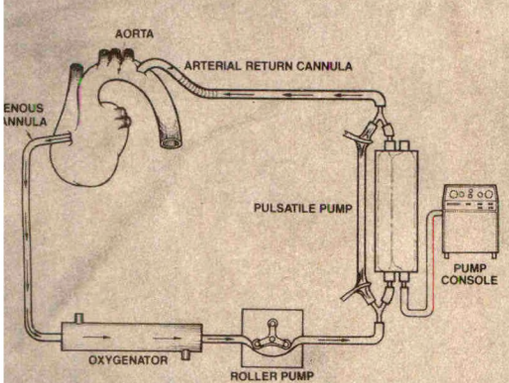


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*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

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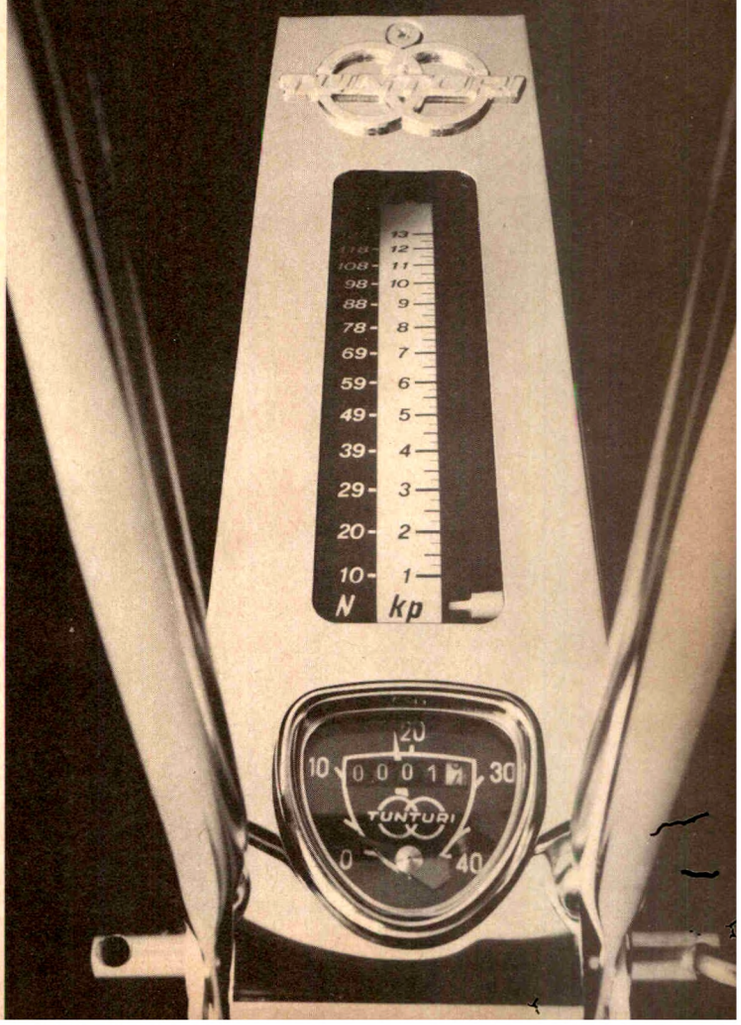
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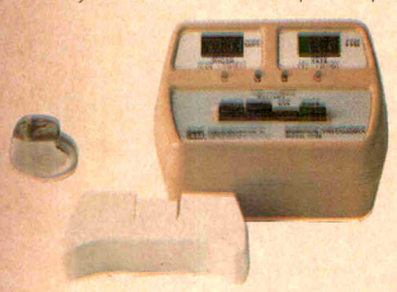
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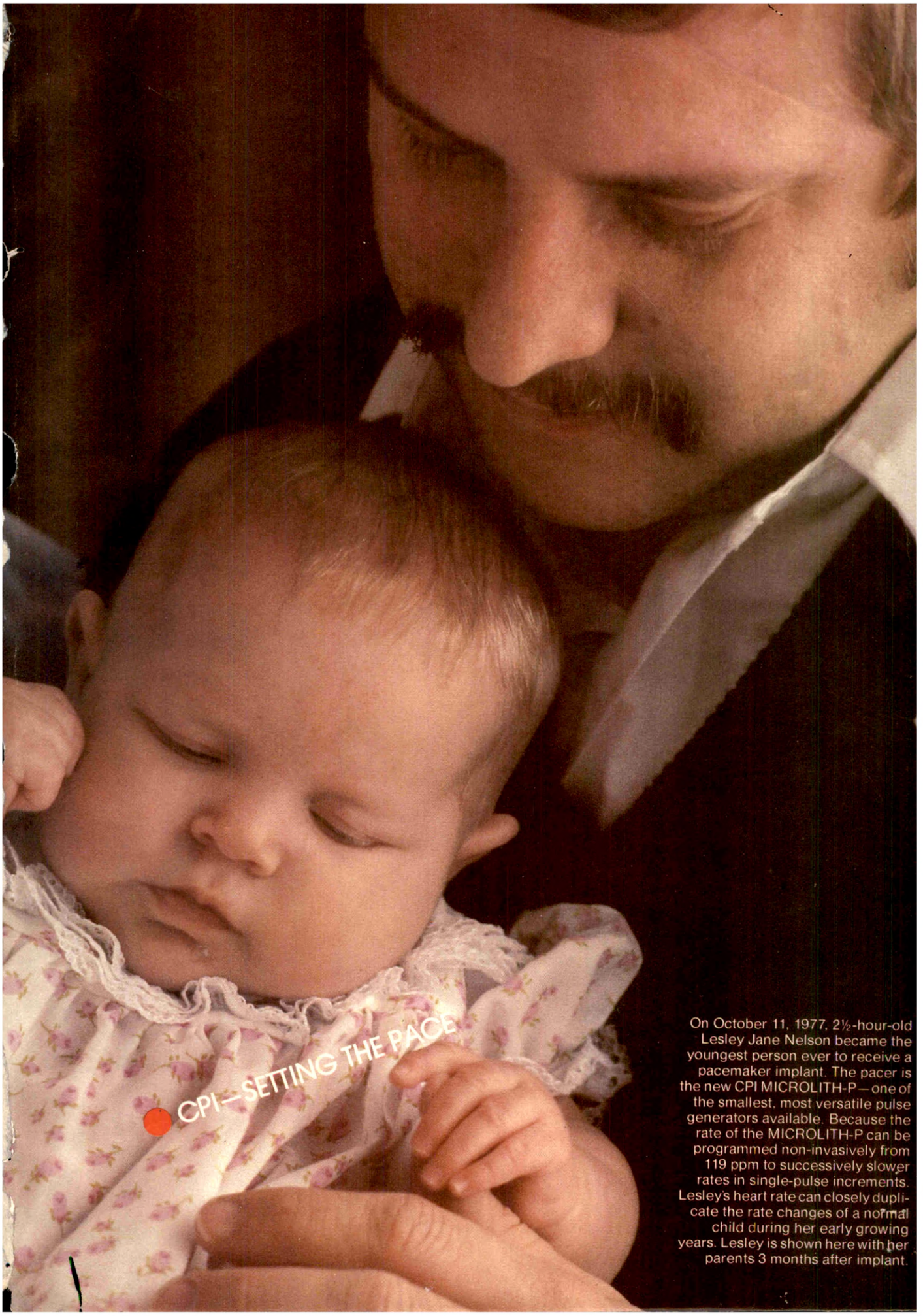


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*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 50.

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